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Welcome

Greetings and welcome to our fourth and final edition of the *European Medical Journal* for 2016. A round-up of pioneering insights and updates from across the past year, we present a collection of peer-reviewed articles for your perusal, in addition to this edition's feature article highlighting a pertinent topic for implementation within disease research and daily practice moving forward.

Within this issue's multidisciplinary tour, Bazarbachi et al. call for a better understanding of the molecular phenomena originating from the onset of non-transfusion-dependent thalassaemia, a group of syndromes whose incidence within the developing world are increasing at an alarming rate. Daneault et al. initially outline current treatment approaches for Parkinson's disease-associated drug-induced dyskinesia, moving on to examine a recent suggestion that treatment should focus on the impact on patients' daily activities rather than the presence of the condition. The benefits of this approach for both the patient and their caregiver are showcased. An important matter rarely brought to light, Masjedi et al. review occupational work-related allergic disorders which require early diagnosis to prevent long-term consequences, while on a similar topic Steveling-Klein addresses the factors involved in successful utilisation of allergen-specific immunotherapy, touching upon application routes, immunomodulatory mechanisms, indications, safety, efficacy, and cost-effectiveness. Focussing on Type 2 diabetes mellitus, Martín-Timón et al. explain the importance of managing cardiovascular risk factors in patients.

Additionally, van der Berg et al. provide this edition's feature article, continuing with the subject of diabetes. With an ever-growing body of evidence reflecting the adverse effects of sedentary behaviour on disease risk, the authors discuss the barriers facing researchers investigating the influences of sedentary behaviour. Although a significant risk factor, currently no recommendations regarding sedentary behaviour are included in the prevention regimens given to high-risk Type 2 diabetes mellitus patients. This concern and its potential impact on future public health are emphasised.

We hope you enjoy this edition of our renowned *European Medical Journal* and that the eJournal will prove both timely and valuable. Drawing upon a range of therapeutic areas, we are sure there will be something for everyone and the opportunity to consider new areas of interest. Eagerly looking forward to the sensational innovations 2017 will undoubtedly bring, we hope you continue with us as we traverse the medical ambit in next year's issues and as always, thank you for your support.

Spencer Gore

Director, European Medical Journal

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Foreword

Prof László Vécsei

Director, Department of Neurology, University of Szeged, Szeged, Hungary.

Dear Colleagues,

May I take this opportunity to sincerely welcome you to the fourth and final edition of our flagship mixed therapeutic area publication, *European Medical Journal*, of 2016. With the nights rapidly drawing in and the holiday season within grasp, this issue provides an overview of focusses from the past year's medical ventures, spanning an expanse of topics relevant to both clinical practice and research alike. In such a technologically-advanced era, the discovery of novel mechanisms and routes of pathogenesis not only quench our increasing intrigue, but also play testament to the improvement of patient therapy, diagnosis, and quality of life. It is these attributes that our eJournal aims to capture for your leisure and enjoyment.

Included within, van der Berg et al. author the feature article provided in this edition, highlighting the role of sedentary behaviour on adverse health and disease development. An ever-increasing burden on the healthcare system, conditions related to long periods of sedentary behaviour including metabolic syndrome and Type 2 diabetes are rising in incidence across the Western world. Along with a snapshot of barriers impeding research in the area, the authors stress the need for alteration of the sedentary behaviour timeline within clinical practice.

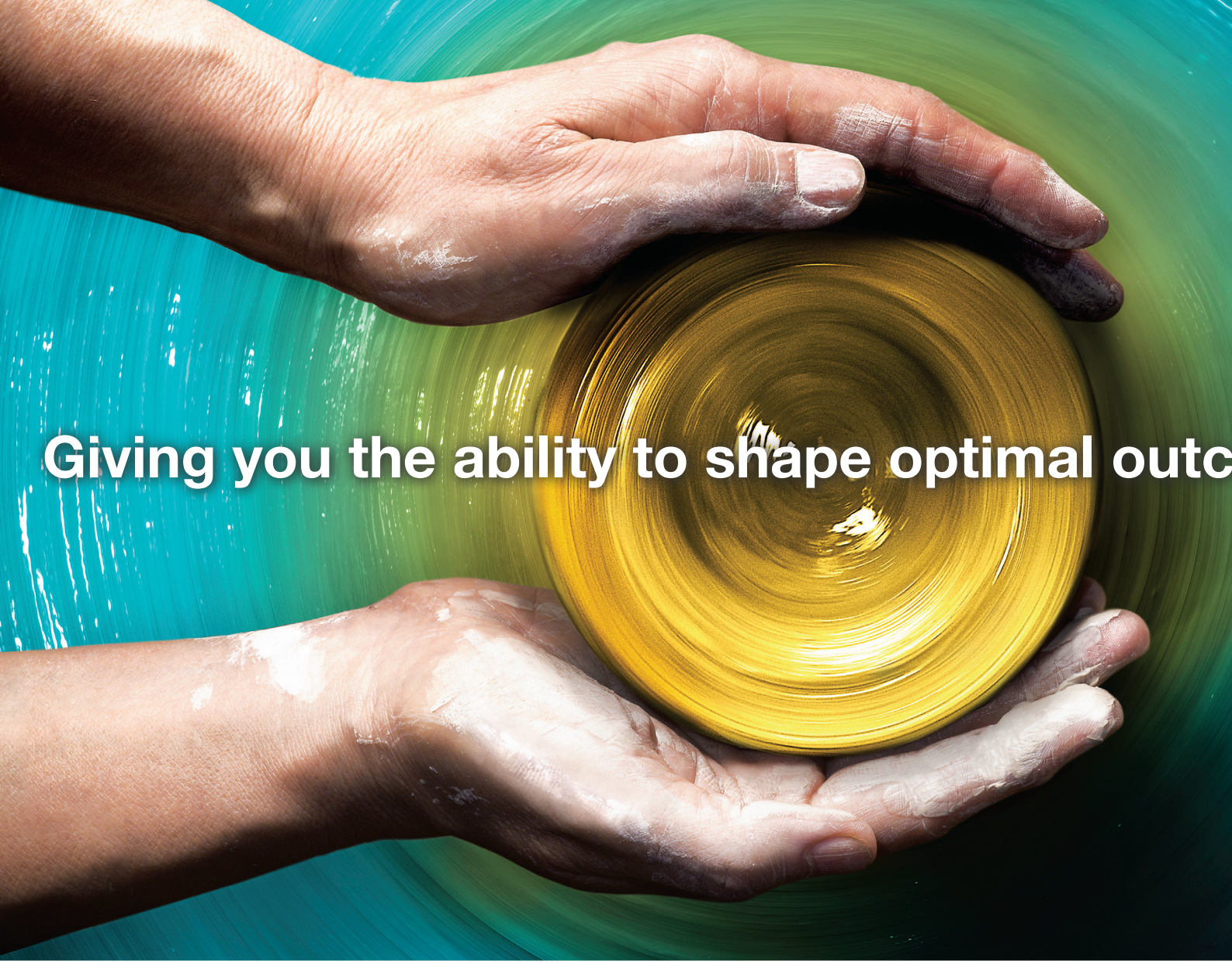
> “In such a technologically-advanced era, the discovery of novel mechanisms and routes of pathogenesis not only quench our increasing intrigue, but also play testament to the improvement of patient therapy, diagnosis, and quality of life.”

Constituents of a plethora of innovative research presented across recent years, the peer-reviewed, high quality articles included range from the pathology of allergy, its treatment using immunotherapy, and how occupational work may aggravate an already complicated condition, to the management of Parkinson's disease-associated drug-induced dyskinesia. Others call for better understanding of disease management and risk factors that could, and should, be targeted prior to onset of Type 2 diabetes mellitus and non-transfusion-dependent thalassaemia.

Excited for the medical developments which are sure to be announced within 2017, my fellow editorial board members and myself hope that you relish reading this edition of *European Medical Journal* and that you find it both interesting and applicable within your daily practice.

László Vécsei

Director, Department of Neurology, University of Szeged, Szeged, Hungary; Past Regional Vice-President of the European Federation of Neurological Societies; General Secretary of Danube Neurology Symposium.



Abbreviated Prescribing Informationx:

▼ Revlimid® (lenalidomide) 2.5mg, 5mg, 7.5mg, 10mg, 15mg, 20 mg and 25mg hard capsules. Refer to the Summary of Product Characteristics (SmPC) before prescribin g. **Name of medicine:** Revlimid**. Active ingredients:** lenalidomide. **List of excipients**: Capsule contents: Lactose, anhydrous, cellulose, microcrystalline, croscarmellose sodium, magnesium stearate. Capsule shell: gelatin, titanium dioxide (E171), indigo carmine (E132), yellow iron oxide (E172). Printing ink: shellac, propylene glycol, black iron oxide (E172), potassium hydroxide. **Available dosage forms:** Hard capsules containing lenalidomide 2.5mg, 5mg, 7.5mg, 10mg, 15mg, 20mg or 25mg. **Authorized indications**: Multiple myeloma: Revlimid is indicated for the treatment of adult patients with previously untreated multiple myeloma who are not eligible for transplant. Revlimid in combination with dexamethasone is indicated for the treatment of multiple myeloma in adult patients who have received at least one prior therapy. Myelodysplastics syndromes (MDS): Revlimid is indicated for the treatment of patients with transfusion-dependent anaemia due to low- or intermediate-1-risk myelodysplastic syndromes associated with an isolated deletion 5q cytogenetic abnormality when other therapeutic options are insufficient or inadequate. Mantle cell lymphoma (MCL): Revlimid is indicated for the treatment of adult patients with relapsed or refractory mantle cell lymphoma. **Dosage regimens and routes of administration:** Newly diagnosed multiple myeloma (NDMM). *Lenalidomide in combination with dexamethasone until disease progression in patients who are not eligible for transplant.* Lenalidomide treatment must not be started if the Absolute Neutrophil Count (ANC) is < 1.0 x 10^9/L, and/or platelet counts are < 50 x 10^9/L. The recommended starting dose of lenalidomide is 25 mg orally once daily on days 1-21 of repeated 28-day cycles. The recommended dose of dexamethasone is 40 mg orally once daily on days 1, 8, 15 and 22 of repeated 28-day cycles. Patients may continue lenalidomide and dexamethasone therapy until disease progression or intolerance. Dosing is continued or modified based upon clinical and laboratory findings. Recommended dose adjustments during treatment and restart of treatment: Dose adjustments are recommended to manage grade 3 or 4 thrombocytopenia, neutropenia, or other grade 3 or 4 toxicity judged to be related to lenalidomide. *Lenalidomide in combination with melphalan and prednisone followed by maintenance monotherapy in patients who are not eligible for transplant.* Lenalidomide treatment must not be started if the ANC is < 1.5 x 10^9/L, and/or platelet counts are < 75 x 10^9/L. The recommended starting dose is lenalidomide 10 mg/day orally on days 1-21 of repeated 28-day cycles for up to 9 cycles, melphalan 0.18 mg/kg orally on days 1-4 of repeated 28 day cycles, prednisone 2 mg/kg orally on days 1-4 of repeated 28-day cycles. Patients who complete 9 cycles or who are unable to complete the combination therapy due to intolerance are treated with lenalidomide alone, 10 mg/day orally on days 1-21 of repeated 28-day cycles given until disease progression. Dosing is continued or modified based upon clinical and laboratory findings. Recommended dose adjustments during treatment and restart of treatment. Dose adjustments are recommended to manage grade 3 or 4 thrombocytopenia, neutropenia, or other grade 3 or 4 toxicity judged to be related to lenalidomide. Multiple myeloma with at least one prior therapy: Lenalidomide treatment must not be started if the ANC < 1.0 x 10^9/l, and/or platelet counts < 75 x 10^9/l or, dependent on bone marrow infiltration by plasma cells, platelet counts < 30 x 10^9/l. The recommended starting dose of lenalidomide is 25mg orally once daily on days 1-21 of repeated 28-day cycles and 40mg dexamethasone orally once daily on days 1-4, 9-12 and 17-20 of each 28-day cycle for the first 4 cycles of therapy and then 40mg once daily on days 1-4 every 28 days. Continue or modify dose based upon clinical or laboratory findings. Prescribing physicians should carefully evaluate which dose of dexamethasone to use, taking into account the condition and disease status of the patient. Dose adjustments are recommended to manage grade 3 or 4 neutropenia or thrombocytopenia, or other grade 3 or 4 toxicity to be related to lenalidomide. MDS: Lenalidomide treatment must not be started if the ANC < 0.5 x 10^9/l and/or platelet counts < 25 x 10^9/l. The recommended starting dose of lenalidomide is 10 mg orally once daily on days 1-21 of repeated 28-day cycles. Dosing is continued or modified based upon clinical and laboratory findings. Dose adjustments, are recommended to manage grade 3 or 4 neutropenia or thrombocytopenia, or other grade 3 or 4 toxicity judged to be related to lenalidomide. MCL: The recommended starting dose of lenalidomide is 25 mg orally once daily on days 1-21 of repeated 28-day cycles. Dosing is continued or modified based upon clinical and laboratory findings. Dose adjustments are recommended to manage grade 3 or 4 neutropenia or thrombocytopenia or other grade 3 or 4 toxicity judged to be related to lenalidomide. All indications: Lenalidomide interruption or discontinuation should be considered for grade 2 or 3 skin rash. Lenalidomide must be discontinued for angioedema, grade 4 rash, exfoliative or bullous rash, or if Stevens-Johnson syndrome (SJS) or toxic epidermal necrolysis (TEN) is suspected, and should not be resumed following discontinuation from these reactions. See Section 4.2 of the SmPC for more information. Discontinuation of lenalidomide for MDS: Patients without at least a minor erythroid response within 4 months of therapy initiation, demonstrated by at least a 50% reduction in transfusion requirements or, if not transfused, a 1g/dl rise in haemoglobin, should discontinue lenalidomide treatment. **Reference to special groups of patients**. *Paediatric population*: Revlimid should not be used in children and adolescents from birth to less than 18 years because of safety concerns *Older people*: NDMM: For patients older than 75 years of age treated with lenalidomide in combination with dexamethasone, the starting dose of dexamethasone is 20 mg/day on Days 1, 8, 15 and 22 of each 28-day treatment cycle. No dose adjustment is proposed for patients older than 75 years treated with lenalidomide in combination with melphalan and prednisone. Because elderly patients are more likely to have decreased renal function, care should be taken in dose selection and it would be prudent to monitor renal function. Other indications: no overall difference in safety and efficacy was observed between patients aged 65 years or over compared with patients aged under 65 years of age. *Renal function impairment:* Lenalidomide is substantially excreted by the kidney, patients with greater degrees of renal impairment can have impaired treatment tolerance. Care should be taken in dose selection and monitoring of renal function is advised. No dose adjustments are required for patients with mild renal impairment. Dose adjustments for patients with moderate or severe renal impairment or end stage renal disease are advised. For full details please refer to the SmPC. **Contraindications**: Hypersensitivity to the active substance or to any of the excipients. Pregnancy and women of childbearing potential who do not meet all of the conditions of the Pregnancy Prevention Programme (PPP). **Warnings:** Pregnancy warning: If Revlimid is taken during pregnancy a teratogenic effect in humans is expected. All female patients or male patients with a female partner of childbearing potential must fulfil the conditions of the PPP. Refer to Section 4.4 of SmPC for a full list of the criteria for women of non-childbearing potential. Female patients must understand the expected teratogenic risk to the unborn child and the need for effective contraception without interruption. She must be capable of complying with effective contraception and understand the need to undergo medically supervised pregnancy tests. See Section 4.4 of the SmPC for examples of suitable methods of contraception. Combined oral contraceptive pills are not recommended because of the increased risk of venous thromboembolism in multiple myeloma patients taking Revlimid in combination therapy, and to a lesser extent in patients with MDS and MCL taking lenalidomide monotherapy. If a patient is currently using combined oral contraception the patient should switch to one of the effective methods listed in Section 4.4 of the SmPC. This risk continues 4-6 weeks after discontinuation of combined oral contraception. The efficacy of contraceptive steroids may be reduced during co-administration with dexamethasone. Implants and levonorgestrel-releasing intrauterine systems are suitable methods of contraception. These are however associated with an increased risk of infection at the time of insertion and irregular vaginal bleeding. Prophylactics antibiotics should therefore be considered particularly in patients with neutropenia. Copper-releasing intrauterine devices are generally not recommended due to the potential risk of infection at the time of insertion and menstrual loss which may compromise patients with neutropenia or thrombocytopenia. Male patients must understand the teratogenic risk of sexual activity with a pregnant woman or a woman of childbearing potential not using effective contraception (even if the man has had a vasectomy) and as a precaution, he must use a condom throughout treatment duration, during dose interruption and for 1 week after dose interruptions and/or cessation of treatment. Male patients must understand that if his female partner becomes pregnant whilst he is taking Revlimid or shortly after he has stopped taking Revlimid, he should inform his treating physician immediately and that it is recommended to refer the female partner to a physician specialised or experienced in teratology for evaluation and advice. Patients should not donate blood during therapy or for 1 week following discontinuation of Revlimid. As part of the PPP, physicians and pharmacists should comply with the procedures in place in their country. For full details, please refer to the SmPC. Further information is also available from Celgene. Other special warnings and precautions: *Myocardial infarction*: Myocardial infarction has been reported in patients receiving lenalidomide, particularly in those with known risk factors and within the first 12 months when used in combination with dexamethasone. Patients with known risk factors – including prior thrombosis – should be closely monitored, and action should be taken to try to minimize all modifiable risk factors (eg. smoking, hypertension, and hyperlipidaemia). *Venous and arterial thromboembolic events*: In patiens with multiple myeloma, the combination of lenalidomide and dexamethasone is associated with an increased risk of venous thromboembolism (predominantly deep vein thrombosis [DVT] and pulmonary embolism) and arterial thromboembolism (predominantly myocardial infarction and cerebrovascular event). Venous thromboembolism was seen to a lesser extent with lenalidomide in combination with melphalan and prednisone in NDMM and with monotherapy in MDS. In patients with MDS and MCL treatment with lenalidomide monotherapy was also associated with a risk of venous thromboembolism (predominantly deep vein thrombosis and pulmonary embolism), but to a lesser extent than in patients with multiple myeloma. Consequently, patients with known risk factors for thromboembolism – including prior thrombosis – should be closely monitored. Concomitant administration of erythropoietic agents or previous history of thromboembolic events may also increase thrombotic risk in these patients. Erythropoietic agents or hormone replacement therapy should be used with caution. A haemoglobin concentration of above 12g/dl should lead to discontinuation of erythropoietic agents. Patients and physicians are advised to

Revlimid®
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10 mg is the recommended starting dose for patients with MDS isolated del(5q)[1]*

- REVLIMID® is associated with a rapid and sustained achievement of RBC-TI compared with placebo[2]
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*Recommended starting dose for patients with normal renal function/mild renal impairment (CLcr ≤60 mL/min)

1. REVLIMID® Summary of Product Characteristics, 2016. Approved MDS indication: Revlimid is indicated for the treatment of patients with transfusion-dependent anaemia due to low- or intermediate-1-risk myelodysplastic syndromes associated with an isolated deletion 5q cytogenetic abnormality when other therapeutic options are insufficient or inadequate. The recommended starting dose of lenalidomide is 10 mg orally once daily on days 1–21 of repeated 28-day cycles.

2. Giagounidis A. *et al. Eur J Haematol* 2014;93:429-38.

be observant for the signs and symptoms of thromboembolism. Prophylactic antithrombotic medicines should be recommended, especially in patients with additional risk factors. If the patient experiences any thromboembolic events, treatment must be discontinued and standard anticoagulation therapy started. Once any complications of the thromboembolic event have been managed, lenalidomide treatment may be restarted at the original dose dependent upon a benefit risk assessment – anticoagulation therapy should continue during the course of lenalidomide treatment (see Section 4.4 of the SmPC). *Neutropenia and thrombocytopenia:* The major dose limiting toxicities of lenalidomide include neutropenia and thrombocytopenia. A complete blood cell count, including white blood cell count with differential count, platelet count, haemoglobin, and haematocrit should be performed at baseline, every week for the first 8 weeks of lenalidomide treatment and monthly thereafter to monitor for cytopenias. In MCL patients, the monitoring scheme should be every 2 weeks in cycles 3 and 4, and then at the start of each cycle. A dose reduction may be required (see section 4.2 of the SmPC). In case of neutropenia, the physician should consider the use of growth factors in patient management. Patients should be advised to promptly report febrile episodes. Co-administration of lenalidomide with other myelosuppressive agents should be undertaken with caution.Patients and physicians are advised to be observant for signs and symptoms of bleeding, including petechiae and epistaxes, especially in patients receiving concomitant medicinal products susceptible to induce bleeding. NDMM: The combination of lenalidomide with melphalan and prednisone is associated with a higher incidence of grade 4 neutropenia and grade 3 and 4 thrombocytopenia. Multiple Myeloma with at least one prior therapy: The combination of lenalidomide and dexamethasone is associated with a higher incidence of grade 4 neutropenia and grade 3 and 4 thrombocytopenia. MDS: Lenalidomide treatment in MDS patients is associated with a higher incidence of grade 3 and 4 neutropenia and thrombocytopenia compared to patients on placebo. MCL: Lenalidomide treatment in MCL patients is associated with a higher incidence of grade 3 and 4 neutropenia compared with patients on the control arm. *Infection with or without neutropenia* Patients with multiple myeloma are prone to develop infections including pneumonia. A higher rate of infections was observed with lenalidomide in combination with dexamethasone than with MPT. Grade ≥ 3 infections occurred within the context of neutropenia in less than one-third of the patients. Patients with known risk factors for infections should be closely monitored. All patients should be advised to seek medical attention promptly at the first sign of infection (eg, cough, fever, etc) thereby allowing for early management to reduce severity. *Renal impairment:* Care should be taken in dose selection and monitoring of renal function is advised. *Thyroid disorders:* Cases of hypothyroidism and cases of hyperthyroidism have been reported. Optimal control of co-morbid conditions influencing thyroid function is recommended before start of treatment. Baseline and ongoing monitoring of thyroid function is recommended. *Peripheral neuropathy:* Lenalidomide is structurally related to thalidomide, which is known to induce severe peripheral neuropathy. There was no increase in peripheral neuropathy observed with long term use of lenalidomide for the treatment of NDMM. *Tumour flare reaction and tumour lysis syndrome:* Because lenalidomide has anti-neoplastic activity the complications of tumour lysis syndrome (TLS) may occur. TLS and tumour flare reaction (TFR) have commonly been observed in patients with chronic lymphocytic leukemia (CLL), and uncommonly in patients with lymphomas, who were treated with lenalidomide. Fatal instances of TLS have been reported during treatment with lenalidomide. The patients at risk of TLS and TFR are those with high tumour burden prior to treatment. Caution should be practiced when introducing these patients to lenalidomide. These patients should be monitored closely, especially during the first cycle or dose-escalation, and appropriate precautions taken. There have been rare reports of TLS in patients with MM treated with lenalidomide, and no reports in patients with MDS treated with lenalidomide. *MCL:Tumour burden:* Lenalidomide is not recommended for the treatment of patients with high tumour burden if alternative treatment options are available. *Tumour flare reaction:* Careful monitoring and evaluation for TFR is recommended. Patients with high MCL International Prognostic Index (MIPI) at diagnosis or bulky disease (at least one lesion that is ≥ 7 cm in the longest diameter) at baseline may be at risk of TFR. Tumour flare reaction may mimic progression of disease (PD). The decision to take therapeutic measures for TFR should be made after careful clinical assessment of the individual patient. *Allergic Reactions:* Cases of allergic reaction/hypersensitivity reactions have been reported in patients treated with lenalidomide. *Severe skin reactions:* SJS and TEN have been reported. *Lactose intolerance:* Revlimid capsules contain lactose. Patients with rare hereditary problems of galactose intolerance, the Lapp lactase deficiency or glucose-galactose malabsorption should not take this medicinal product. *Unused capsules*: Patients should be advised never to give this medicinal product to another person and to return any unused capsules to their pharmacist at the end of the treatment. *Second Primary Malignancies (SPM):* In patients receiving lenalidomide in combination with dexamethasone until progression or for 18 months, the hematologic SPM incidence rate (0.16 per 100 person-years) was not increased as compared to thalidomide in combination with melphalan and prednisone (0.79 per 100 person-years). The risk of occurrence of hematologic SPM must be taken into account before initiating Revlimid either in combination with melphalan or immediately following high-dose melphalan and Autologous Stem Cell Transplant. Physicians should carefully evaluate patients before and during treatment using standard cancer screening for occurrence of SPM and institute treatment as indicated See section 4.4 of the SmPC. *Progression to acute myeloid leukaemia in low- and intermediate-1-risk MDS.* Karyotype: Baseline variables including complex cytogenetics are associated with progression to AML in subjects who are transfusion dependent and have a Del (5q) abnormality. In a clinical trial of Revlimid in low- or intermediate-1-risk MDS, subjects who had a complex cytogenetics had the highest estimated 2-year cumulative risk of progression to AML (38.6%). The estimated 2-year rate of progression to AML in patients with an isolated Del (5q) abnormality was 13.8%, compared to 17.3% for patients with Del (5q) and one additional cytogenetic abnormality. As a consequence, the benefit/risk ratio of Revlimid when MDS is associated with Del (5q) and complex cytogenetics is unknown. TP53 status: A TP53 mutation is present in 20 to 25% of lower-risk MDS Del 5q patients and is associated with a higher risk of progression to acute myeloid leukaemia (AML). In a post-hoc analysis of a clinical trial of Revlimid in low- or intermediate-1-risk MDS (MDS-004), the estimated 2-year rate of progression to AML was 27.5 % in patients with IHC-p53 positivity (1% cut-off level of strong nuclear staining, using immunohistochemical assessment of p53 protein as a surrogate for TP53 mutation status) and 3.6% in patients with IHC-p53 negativity (p=0.0038). *Progression to other malignancies in MCL:* AML, B-cell malignancies and non-melanoma skin cancer (NMSC) are potential risks. *Hepatic disorders:* Hepatic failure, including fatal cases, has been reported in patients treated with lenalidomide in combination therapy. Monitoring of liver function is recommended. Newly diagnosed multiple myeloma patients; There was a higher rate of intolerance (grade 3 or 4 adverse events, serious adverse events, discontinuation) in patients with age > 75 years, ISS stage III, ECOG PS≤2 or CLcr<60 mL/min when lenalidomide is given in combination. Patients should be carefully assessed for their ability to tolerate lenalidomide in combination, with consideration to age, ISS stage III, ECOG PS≤2 or CLcr<60 mL/min. *Cataract.* Cataract has been reported with a higher frequency in patients receiving lenalidomide in combination with dexamethasone particularly when used for a prolonged time. Regular monitoring of visual ability is recommended. **Clinically significant interactions:** Lenalidomide is not an enzyme inducer, therefore induction leading to reduced efficacy of drugs, including hormonal contraceptives is not expected. However, dexamethasone is known to be a moderate enzyme inducer and it may not be excluded that the efficacy of oral contraceptives may be reduced during treatment. Effective measures to avoid pregnancy must be taken. The effect of dexamethasone on warfarin is unknown and close monitoring of warfarin concentration is advised during treatment. Concomitant administration with lenalidomide 10 mg/day increased the plasma exposure of digoxin. It is not known whether the effect will be different in the therapeutic situation. Therefore, monitoring of the digoxin concentration is advised during lenalidomide treatment. There is an increased risk of rhabdomyolysis when statins are administered with lenalidomide, which may be simply additive. Enhanced clinical and laboratory monitoring is warranted notably during the first weeks of treatment. **Reported side effects:** For NDMM in patients treated with lenalidomide in combination with low dose dexamethasone: The most frequently observed adverse reactions were diarrhoea, fatigue, back pain, asthenia, insomnia, rash, decreased appetite, cough, pyrexia, and muscle spasms. For NDMM patients treated with lenalidomide in combination with melphalan and prednisone: The most frequently observed adverse reactions were febrile neutropenia, anaemia, thrombocytopenia, leukopenia, constipation, diarrhoea, rash, pyrexia, peripheral oedema, cough, decreased appetite, and asthenia. For multiple myeloma with at least one prior therapy: The most frequently observed adverse reactions were fatigue, neutropenia, constipation, diarrhoea, muscle cramp, anaemia, thrombocytopenia and rash. For MDS the most commonly observed adverse reactions were neutropenia, thrombocytopenia, diarrhoea, constipation, nausea, pruritus, rash, fatigue and muscle spasms. For MCL: The most frequently observed adverse reactions were neutropenia, anaemia, diarrhea, fatigue, constipation, pyrexia and rash. Other side-effects seen on treatment with lenalidomide combination therapy, monotherapy and post-marketing are listed in the SmPC. **Storage condition:** This medicinal product does not required any special storage conditions. **Price**:xxx **Classification:** Prescription only. **Marketing Authorisation Holder:** Celgene Europe Limited, 1 Longwalk, Stockley Park, Uxbridge, UB11 1DB, United Kingdom. **Marketing Authorisation Numbers:** Revlimid 2.5mg hard capsules EU/1/07/391/005, EU/1/07/391/007, Revlimid 5mg hard capsules EU/1/07/391/001, EU/1/07/391/008, Revlimid 7.5mg hard capsules EU/1/07/391/006, Revlimid 10mg hard capsules EU/1/07/391/002, Revlimid 15mg hard capsules EU/1/07/391/003, Revlimid 20mg hard capsules EU/1/07/391/009, Revlimid 25mg hard capsules EU/1/07/391/004 **Internal ID of the printed material:** INT-VID160009**. Date of last revision**: 08 July 2016.

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SEDENTARY BEHAVIOUR: A NEW TARGET IN THE PREVENTION AND MANAGEMENT OF DIABETES?

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INTRODUCTION

Since the early 2000s, an increasing number of studies have focussed on the adverse health effects of sitting. Sitting, together with other activities characterised by a low energy expenditure while being in a sitting or reclining position, such as watching television (TV) or using the computer, are denoted as sedentary behaviour.[1] It has been shown that adults spend up to 60% of their waking hours in sedentary positions.[2] Large amounts of sedentary behaviour have been associated with unfavourable levels of cholesterol and triacylglycerol,[3-5] markers of insulin resistance,[3,5,6] and metabolic syndrome.[4,7-9] Interestingly, these associations have been demonstrated to be independent of moderate-to-vigorous physical activity. Notably, it may be possible that high levels of daily physical activity attenuate or reduce the adverse effects of sitting on metabolic outcomes. However to date, such effects of high levels of physical activity have only been demonstrated for the increased mortality risks associated with high total sitting time.[10]

In contrast to physical activity, sedentary behaviour is currently not incorporated in the prevention and management strategies of Type 2 diabetes mellitus (T2DM). Since sedentary behaviour has consistently been associated with risk factors for T2DM and the majority of adults spend most of the day being sedentary,[2,11] it could be argued that this behaviour may also be relevant for the prevention and treatment of the disease. This paper therefore provides an overview of the current sedentary behaviour literature in order to provide insight into its importance in the prevention and management of T2DM. First, we discuss the possibilities and issues of the measurement of sedentary behaviour, then the evidence linking sedentary behaviour to T2DM will be provided, as well as the underlying biological mechanisms. Finally, we consider directions for future research and implications for public health and clinical practice.

SEDENTARY BEHAVIOUR MEASUREMENT: ACCELEROMETRY

The measurement of sedentary behaviour has usually been based on self-reporting methods, such as questionnaires (self-administered or interviewer-administered), diaries, and short-term recalls. Questionnaires that focus on a specific domain, for example leisure time, or a specific type of sedentary behaviour, for example watching TV, have most often been used. Although TV viewing time can be seen as a significant part of the total daily sedentary time,[12] it is not entirely representative; other types of sedentary behaviour, for example using the computer or travelling by car, bus, or train, should also be taken into account. Also, specific domains cannot account for the whole day. Furthermore, self-reporting methods are limited due to issues of recall and reporting bias.[13,14] Nevertheless, TV viewing has shown to be strongly and consistently associated with several adverse outcomes, including metabolic syndrome,[9,15-17] T2DM,[18,19] cardiovascular disease,[18-20] and premature mortality.[18,19,21]

During the late 2000s, accelerometry was introduced within observational studies on physical

activity and sedentary behaviour. This provided researchers with a measurement tool able to overcome the limitations of self-reporting methods. Accelerometers are small, lightweight, portable devices that provide information on the frequency, duration, and intensity of activity of an individual.[13,14] The ActiGraph accelerometer (ActiGraph, Fort Walton Beach, Florida, USA) is a commonly used device usually worn on the waist or hip during waking hours for the duration of 1 week. The device measures motion (acceleration) in three directions: vertical (up-and-down), anteroposterior (back-to-front), and mediolateral (side-to-side). Usually, acceleration data of the vertical direction are used to determine activity levels by converting the raw acceleration data into 'counts'. These counts are summed for a specific time period, usually a minute, and these counts per minute (cpm) are then used to classify activity; the more cpm, the higher the activity intensity. For each type of activity, ranging from sedentary behaviour to high intensity physical activity, specific value ranges have been determined. Since sedentary behaviour is characterised by low intensity levels, <100 cpm is usually used to identify sedentary time.[22] In contrast, moderate-to-vigorous physical activity, such as running, is characterised by high intensity activity levels and identified when ≥2,020 cpm are recorded.[23]

The cut-off point of <100 cpm to identify sedentary time has been widely used, however classification of sedentary time based on acceleration (activity counts) only could easily result in misclassification. For example, when standing still activity counts are low, which will also be seen when sedentary. Thus when activity counts are low (e.g. <100 cpm), the actual behaviour executed could be standing still, but could also be sedentary time. The validity of a cut-off point of <100 cpm to classify sedentary time is thus limited when only acceleration data are used.[24,25] To obtain more accurate estimations of sedentary behaviour, posture-based data should be used. The activPAL™ physical activity monitor (PAL Technologies, Glasgow, UK) is an accelerometer that measures both acceleration and posture and is usually attached directly to the skin on the front of the thigh. Therefore, it can accurately detect a sedentary (sitting/lying) posture (horizontal thigh) versus an upright posture (vertical thigh). The assessment of sedentary time using this technology has indeed been shown to be more accurate than the assessment of sedentary time based only on low activity counts.[25,26] Furthermore, due to the small dimensions of the activPAL and the possibility of a waterproof attachment, a complete assessment of all daily activity, 24 hours per day on multiple days, is feasible.

As well as the total amount of sedentary time per day, accelerometers can be used to assess other constructs of sedentary behaviour such as sedentary behaviour patterns, i.e. how sedentary time is accumulated, for example, multiple short sedentary periods versus one prolonged period. The parameters used to quantify these patterns are sedentary breaks, sedentary bouts, and average sedentary bout duration (Figure 1). A sedentary break is an interruption of sedentary time, representing the transition from a sedentary to an upright position. A sedentary bout is a continuous sedentary period without interruption, which can have any duration. The average sedentary bout duration is calculated by dividing total sedentary time by the total number of sedentary bouts. In addition, accelerometry can be used to study patterns of sedentary behaviour over time, i.e. through the course of the day, during the week (weekdays versus weekend days), or over a year (seasonal variation).

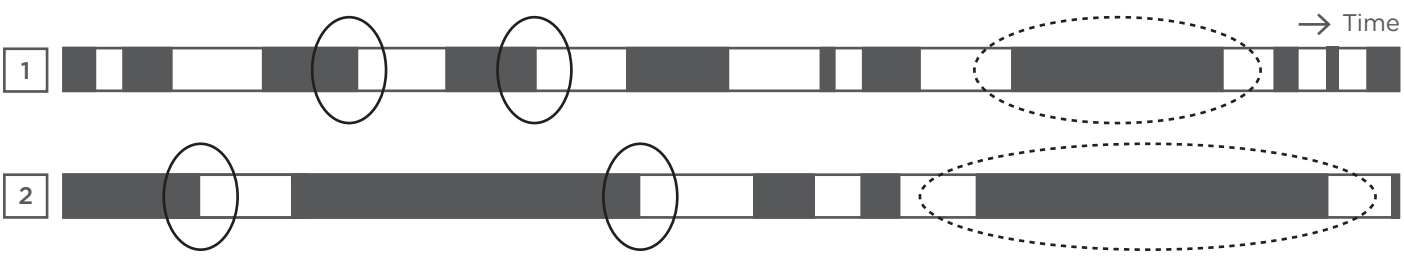

Figure 1: Two examples of sedentary behaviour patterns.
Dark bars indicate sedentary time; light bars indicate non-sedentary time. Solid lines represent sedentary breaks (interruptions of sedentary time); dashed lines represent sedentary bouts (uninterrupted periods of sedentary time).

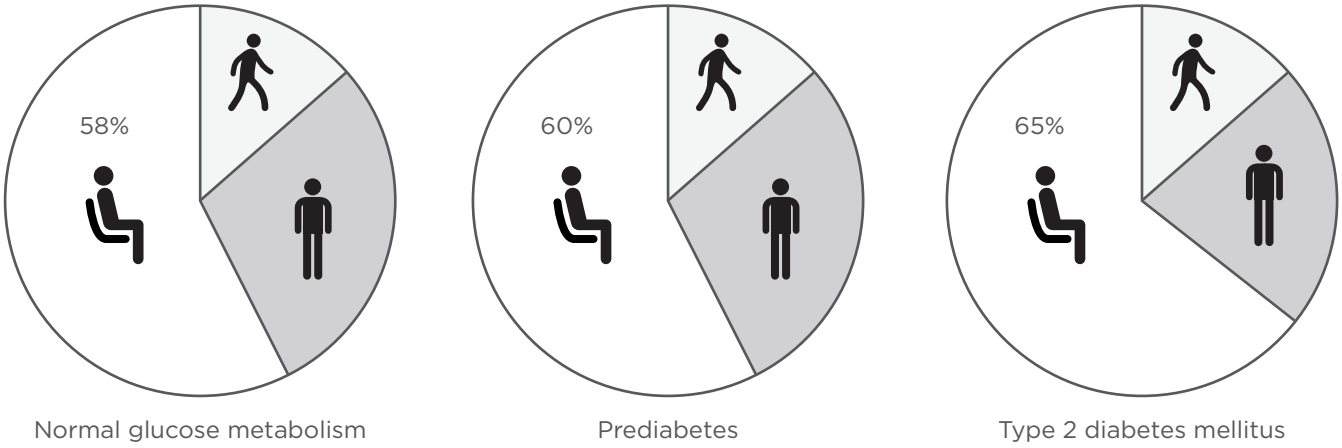

Figure 2: Distribution of waking time spent sedentary, standing, and stepping, according to glucose metabolism status.

SEDENTARY BEHAVIOUR AND TYPE 2 DIABETES MELLITUS

The first study to link sedentary time to diabetes was conducted by Hu et al.[27] in 2001. Within the study, sedentary time (reflected by self-reported TV viewing time) was associated with an increased risk of T2DM. Many other studies using self-reported measures have been published since. These studies have consistently demonstrated an unfavourable association between the amount of sedentary time and T2DM. A meta-analysis that included nine studies using self-reported measures and one study using accelerometry to assess sedentary time demonstrated that larger amounts of time spent sedentary increased the odds of developing metabolic syndrome by 73%.[9] Another meta-analysis showed that sedentary time was associated with a hazard ratio of 1.91 for incident diabetes.[28] In these studies, the role of diet was not incorporated, although high amounts of TV viewing and dietary intake often coexist. However, a recently published study in adolescents did not demonstrate that dietary intake mediated the association between TV viewing and BMI.[29] In contrast, sugar-sweetened beverages and fruit and vegetable intake showed partial mediation effects in conjunction with the TV viewing and metabolic syndrome relationship observed within that study.[29]

Studies using accelerometry to assess sedentary time are scarce. Two studies have used Actigraph[6] and Actiheart®[8] to assess time spent sedentary in British participants with newly diagnosed T2DM (N=528 and N=394, respectively). The studies demonstrated that larger amounts of sedentary time were associated with adverse metabolic outcomes, including waist circumference, high-density lipoprotein (HDL)-cholesterol level, and the level of triacylglycerol.[6,8] Having more sedentary breaks (i.e. more interruptions of sedentary time) was associated with a smaller waist circumference.[6] To our knowledge, only one study has examined the association between posture-based measured sedentary behaviour and T2DM.[30] In our study, we examined both the amount and pattern of sedentary behaviour in 2,497 adults with a normal glucose metabolism, with prediabetes, and with T2DM. We demonstrated that participants with T2DM spent on average 9.7 hours per day in sedentary positions compared to the 9.3 hours of the participants with a normal glucose metabolism and 9.4 hours of participants with prediabetes. This showed that participants with T2DM were sedentary for 65% of their waking time, compared with 58% in participants with a normal glucose metabolism, and 60% in participants with prediabetes (Figure 2). Furthermore, each extra hour of sedentary time was associated with a 22% increased likelihood of T2DM development. The sedentary behaviour pattern was not associated with T2DM or prediabetes, but an association was seen with the diagnosis of metabolic syndrome.

Since sedentary time has been unfavourably associated with risk factors for T2DM and with T2DM itself, studies have started to focus on the effects of reducing sedentary time periods. Reducing sedentary time during waking hours inevitably results in larger amounts of non-sedentary time, which can vary from light physical activity (standing) to vigorous physical

activity (running). The effect of reducing sedentary time may therefore depend on the activity with which it is replaced. Such effects can be examined theoretically using an isotemporal substitution model.[31] To date, two studies have demonstrated, in almost 800 British and Australian participants with newly diagnosed T2DM, that reallocating sedentary time to either light or moderate-to-vigorous intensity activity was associated with reductions in waist circumference and BMI, but not with HDL-cholesterol and glucose levels.[32,33] A few other studies were conducted in non-diabetic, adult populations from the USA (N=923),[34] the UK (N=508),[35] and Australia (N=698),[36] respectively. The studies demonstrated associations with improved markers of insulin sensitivity,[34,35] and improved levels of glucose,[34-36] triacylglycerol,[34,36] and cholesterol.[34-36] In addition, a meta-analysis including 16 experimental studies has provided evidence that breaking up sedentary time by replacing it with light-intensity physical activity has a positive effect on metabolic parameters, including levels of glucose, triglycerides, cholesterol, and insulin.[37] No data have as yet been published on the reallocation effects of sedentary time on cardio-metabolic outcomes, metabolic syndrome, or T2DM in a large sample of adults.

As reducing sedentary time is associated with favourable metabolic health outcomes, the research focus is also on effective strategies to achieve these reductions. A recently published review by Gardner et al.[38] stated that self-monitoring and problem solving were promising techniques and should be used in the development of interventions to reduce sedentary time. Furthermore, sit-to-stand workstations could be used, as it has been shown that such workstations can achieve reductions in sedentary time.[39,40]

BIOLOGICAL MECHANISMS

Due to the relatively recent interest in sedentary behaviour as a risk factor for T2DM and other health outcomes, mechanisms that could explain how sedentary behaviour affects health are largely unknown. Bed rest studies have been used as models to examine the harmful effects of inactivity. Although these models do not accurately reflect daily patterns of sedentary behaviour, such studies do provide leads regarding physiological mechanisms of inactivity. A possible mechanism may be a reduction of lipoprotein lipase due to inactivity of muscle cells, which has been seen in animal studies.[41,42] Since lipoprotein lipase is an essential enzyme that contributes to the metabolism and transport of lipids, it can be hypothesised that a change in activity of this enzyme has a variety of effects on metabolism. Reductions in lipid phosphate phosphatase-1 (LPP1) and decreased adenosine monophosphate-activated protein kinase (AMPK) activity due to inactive muscle cells may also be underlying mechanisms, as both are involved in glucose metabolism.[41] Other possible mechanisms may be changes in vascular function due to the absence of muscular contractions, and increased blood flow. For example, it has been suggested that sedentary behaviour causes low mean shear stress within the vasculature, which may affect endothelial function.[43] In addition, sedentary behaviour may influence the activity of the renin-angiotensin system, which regulates blood pressure and extracellular fluid volume.[44] Lastly, it has been suggested that low-grade inflammation is a pathway through which sedentary behaviour could unfavourably affect health.[45,46] Clearly, physiological studies are warranted to unravel the mechanisms and pathways through which sedentary behaviour affects health.

FUTURE RESEARCH DIRECTIONS

As mentioned earlier, mechanisms and pathways underlying the harmful effects of sedentary behaviour are largely unknown, so there is a need for further physiological studies. In addition, the number of studies that have examined the associations of objectively measured sedentary behaviour with T2DM incidence is limited. Studies using posture-based data in participants with T2DM are thus warranted. These should include longitudinal, dose-response, and intervention studies. Longitudinal studies in which both sedentary behaviour and glucose metabolism status are repeatedly measured over time can provide insight into the temporality of the association. Dose-response studies are needed to obtain insight into the amount of sedentary time that is harmful. Subsequently, intervention studies can provide data on the effectiveness and feasibility of reducing sedentary time with light, moderate, or vigorous activity. Ideally, these studies will also assess information on the type of activity (for example watching TV or doing desk work), the social aspect (with whom), and environmental context (for example, leisure, work, or transportation) as this helps in understanding the nature of sedentary behaviour better.

IMPLICATIONS FOR PUBLIC HEALTH AND CLINICAL PRACTICE

A number of studies have consistently shown that large amounts of sedentary time are associated with several risk factors for T2DM.[3-9] Furthermore, sedentary time has been associated with T2DM itself.[30] Therefore, consideration should be given to developing strategies that reduce the amount of sedentary behaviour in diabetes prevention and management programmes. These strategies should be an addition to those of physical activity as undoubtedly, physical activity is an important factor in the prevention and management of T2DM. Nevertheless, a growing body of evidence shows that sedentary behaviour is a relevant risk factor for health. In addition, sedentary behaviour is highly prevalent on both an inter and intra-individual level, as the majority of individuals have been shown to spend on average more than half of the waking day in sedentary positions.[2] Recommendations regarding sedentary behaviour are thus important in preventing a highly sedentary lifestyle and its adverse effects on health.

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SANGGX.RESP.15.06.0009(1) Date of preparation: July 2016

OPTIMISING RENIN-ANGIOTENSIN-ALDOSTERONE SYSTEM INHIBITOR THERAPY IN HEART FAILURE AND RESISTANT HYPERTENSION: CHALLENGES AND SOLUTIONS

This Lorraine University organised, educational event took place on the 30th August 2016 as a part of the European Society of Cardiology (ESC) Congress in Rome, Italy

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MEETING SUMMARY

Renin-angiotensin-aldosterone system (RAAS) inhibitor therapy has been shown to be beneficial in patients with reduced left ventricular systolic function after an acute myocardial infarction, chronic systolic heart failure, and resistant hypertension. Although RAAS inhibitors are widely regarded as life-saving drugs, their use is often associated with changes in renal function, reducing elimination of potassium from the body. This can result in elevated concentrations of serum potassium, known as hyperkalaemia, which can in turn lead to potentially life-threatening conduction abnormalities and cardiac arrhythmias, and is associated with increased risk of death.

RAAS inhibitors are intrinsically linked to hyperkalaemia, with renin inhibitors, angiotensin-converting enzyme (ACE) inhibitors, angiotensin receptor blockers, and mineral corticoid receptor antagonists all increasing serum potassium levels. The consequences of this side effect are treatment discontinuation or underdosing in patients with heart failure, which may contribute to a higher rate of heart failure-related hospitalisations and deaths. However, since the benefits of RAAS inhibitors outweigh the risks of hyperkalaemia, there remains the need to overcome these challenges rather than withdraw treatment.

Treatment options currently available for reducing potassium concentrations have many limitations, including uncertain efficacy, potential safety issues, as well as the fact that many therapies are temporising,

only reducing serum potassium levels for a short amount of time, rather than eliminating excess potassium from the body. The clinical need to improve hyperkalaemia treatment options has led to the emergence of two novel agents: patiromer, which has been approved in the USA, and sodium zirconium cyclosilicate (SZC) which is currently in the clinical development stage. Studies have shown that these two new agents are efficacious in terms of achieving and maintaining normal potassium levels for up to 1 year and are well tolerated.

Introduction

Treatment with RAAS inhibitors is instrumental in the treatment of patients with heart failure with reduced ejection fraction (HFrEF) to reduce heart failure-related hospitalisations and deaths. According to 2016 European Society of Cardiology (ESC) guidelines, three out of four life-saving drug classes in this patient group have RAAS inhibitor properties.[1] Large-scale randomised clinical trials have demonstrated the critical value of RAAS inhibitors. In a prospective propensity score-matched study of heart patients, all-cause mortality was significantly higher when RAAS inhibitors were not used.[2] Furthermore, in a retrospective study of 205,108 patients, discontinuing RAAS inhibitors or administering them at a submaximal dose was associated with a higher death rate.[3]

The class of RAAS inhibitors is broad, including ACE inhibitors, angiotensin receptor blockers, and aldosterone receptor blockers (Figure 1). However, due to their mechanisms of action, the use of RAAS inhibitors increases serum potassium ion concentrations. Given the risk of hyperkalaemia, RAAS inhibitors are frequently discontinued, underdosed, or just not given to patients with heart failure that are eligible for these life-saving medications.[4] Hence, there is a substantial unmet need for optimisation and maintenance of RAAS inhibitor therapy. Developing novel and better strategies for the management of hyperkalaemia is an integral part of addressing this clinical need.

The issues around optimising RAAS inhibitor therapy in heart failure and resistant hypertension were discussed by international experts at a Lorraine University, Nancy, France, organised, educational event held during the ESC Congress 2016 in Rome. These challenges and solutions included predicting the risk of hyperkalaemia, preventing the development of hyperkalaemia, monitoring serum potassium, and novel agents for treating hyperkalaemia.

Renin-Angiotensin-Aldosterone System and Potassium Homeostasis

RAAS is a complex system that plays a vital role in maintaining arterial blood pressure, water, and electrolyte balance in the body. Renin regulates the first step of the RAAS by converting angiotensinogen to angiotensin I (Figure 1). Angiotensin I is then activated by the enzyme ACE to form angiotensin II.

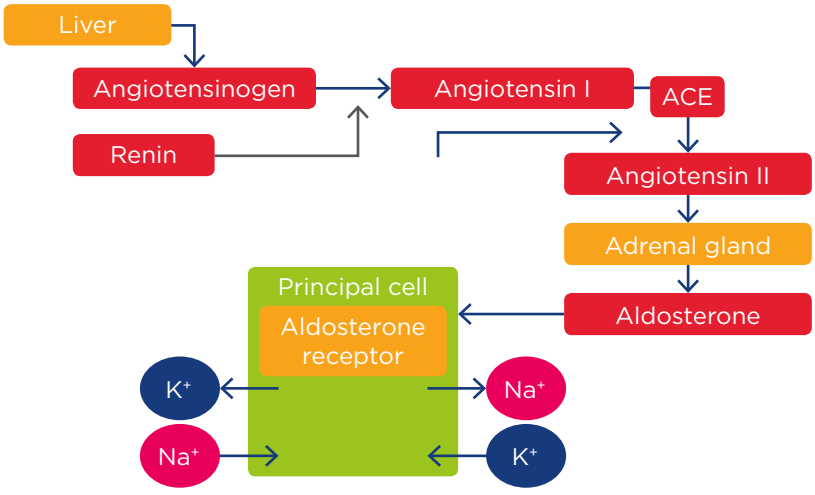

Figure 1: Schematic diagram summarising the renin-angiotensin-aldosterone system.
ACE: angiotensin-converting enzyme.

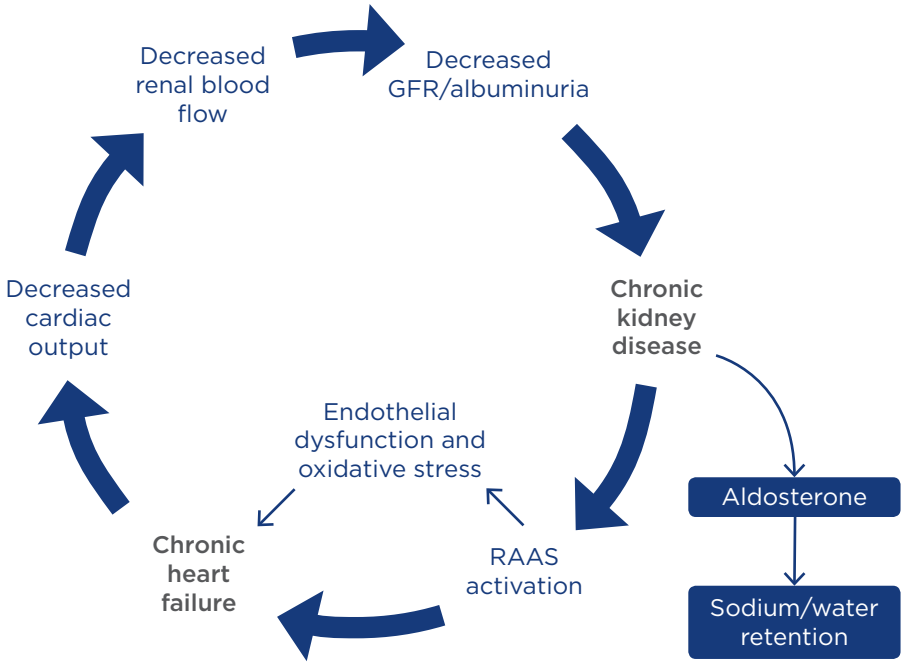

Figure 2: Role of the renin-angiotensin-aldosterone system in chronic heart failure linking to chronic kidney disease.
GFR: glomerular filtration rate; RAAS: renin-angiotensin-aldosterone system.

Angiotensin II, in turn, results in the release of aldosterone. The system is regulated through a negative feedback mechanism.

When RAAS is activated, release of angiotensin II increases sympathetic nervous system activity, inducing endothelial dysfunction and oxidative stress, stimulating vasoconstriction, sodium and water retention, and increasing arterial blood pressure. Furthermore, aldosterone stimulates sodium reabsorption, which in turn causes potassium secretion. Over time this can lead to adverse cardiovascular effects, and ultimately contribute to the development and progression of heart failure (Figure 2). Progressive cardiac dysfunction can in turn lead to reduced renal perfusion (which may further stimulate RAAS activation) thus linking chronic heart failure to chronic kidney disease.[5]

Role of Renin-Angiotensin-Aldosterone System Inhibitors

RAAS inhibitors interfere with the RAAS system at various levels and lead to favourable cardiovascular effects in patients with heart failure. There is much evidence to show that RAAS inhibitors confer significant benefits to patients suffering from HFrEF. Studies have shown that ACE inhibitors, such as enalapril, improved mortality[6] and left ventricular function,[7] while early intervention with captopril prevented or reversed progressive left ventricular remodelling.[8] Angiotensin receptor blockers, such as candesartan, reduced cardiovascular death and hospitalisation for heart failure,[9] while spironolactone improved mortality and hospitalisation in patients with symptomatic heart failure with reduced systolic function,[10] which may in part be due to spironolactone reducing cardiac remodelling.[11] Eplerenone has been demonstrated to reduce cardiovascular death and hospitalisation for heart failure in patients with heart failure symptoms after myocardial infarction and in those with chronic symptomatic heart failure with reduced systolic function,[12] while combined angiotensin receptor blockade and neprilysin inhibition improved cardiovascular morbidity and mortality to a greater extent than using an ACE inhibitor (enalapril) alone.[13]

RAAS inhibitors also have proven clinical benefits in patients with hypertension. A meta-analysis of 26 large scale clinical trials involving 146,838 patients, of which two-thirds were hypertensive, showed that treatment with ACE inhibitors or angiotensin receptor blockers reduced the risk of stroke, heart disease, and heart failure by ≤27%.[14]

RAAS inhibitors were also shown to reduce mortality in hypertensive patients in a meta-analysis of 20 cardiovascular morbidity-mortality trials (N=158,998), where RAAS inhibitor treatment reduced all-cause mortality by 5% (hazard ratio [HR]: 0.95; 95% confidence interval [CI]: 0.91–1.00; p=0.032), and cardiovascular mortality by 7% (HR: 0.93; 95% CI: 0.88–0.99; p=0.018).[15]

Causes and Risks of Hyperkalaemia

As stated above, due to blocking the RAAS system, RAAS inhibitors can cause reduced elimination of potassium by affecting potassium handling in the kidney, subsequently leading to hyperkalaemia.[16] A meta-analysis of five randomised controlled trials involving 553 patients showed that the RAAS inhibitor spironolactone, despite being highly effective at reducing resistant hypertension, raised serum potassium levels.[17] The risks of hyperkalaemia include conduction system abnormalities and serious arrhythmias.[18,19] Furthermore, in epidemiological studies it has been associated with an increased risk of mortality.[20] For example, a retrospective analysis of patients with hypertension and heart failure showed that hyperkalaemia (defined as serum potassium ≥5.1 mEq/L) was associated with increased hospital admissions[21] as well as increased in-hospital mortality.[22]

RAAS inhibitors are tightly linked with increased serum potassium concentrations, and, consequently, hyperkalaemia in HFrEF and hypertensive patients. Hyperkalaemia is common in patients with hypertension taking blood pressure lowering medications, as demonstrated by a 3-year evaluation of 194,456 patients in the Geisinger Health System, USA. Patients using the following medications at baseline showed an increase in risk of hyperkalaemia (defined as potassium >5 mEq/L), of 54% with ACE inhibitors, 13% with β-blockers and 7% with angiotensin receptor blockers.[23] Although much less frequently used, potassium-sparing diuretics (including aldosterone antagonists, amiloride, and triamterene) were not associated with an increase in risk (HR: 1.00, 95% CI: 0.91–1.10). Loop/thiazide diuretic use at baseline was associated with a decrease in risk for hyperkalaemia.[23] A similar trend was seen with the ACE inhibitor lisinopril in 118 male patients with mild-to-moderate essential hypertension, where reduction in blood pressure was associated with significantly increased serum potassium.[24] Estimates of the incidence of hyperkalaemia in patients with HFrEF who have been treated with optimal medical therapy vary substantially, although it is widely acknowledged that reported rates in clinical trials are an underestimation of the actual rates of hyperkalaemia in clinical practice.[25]

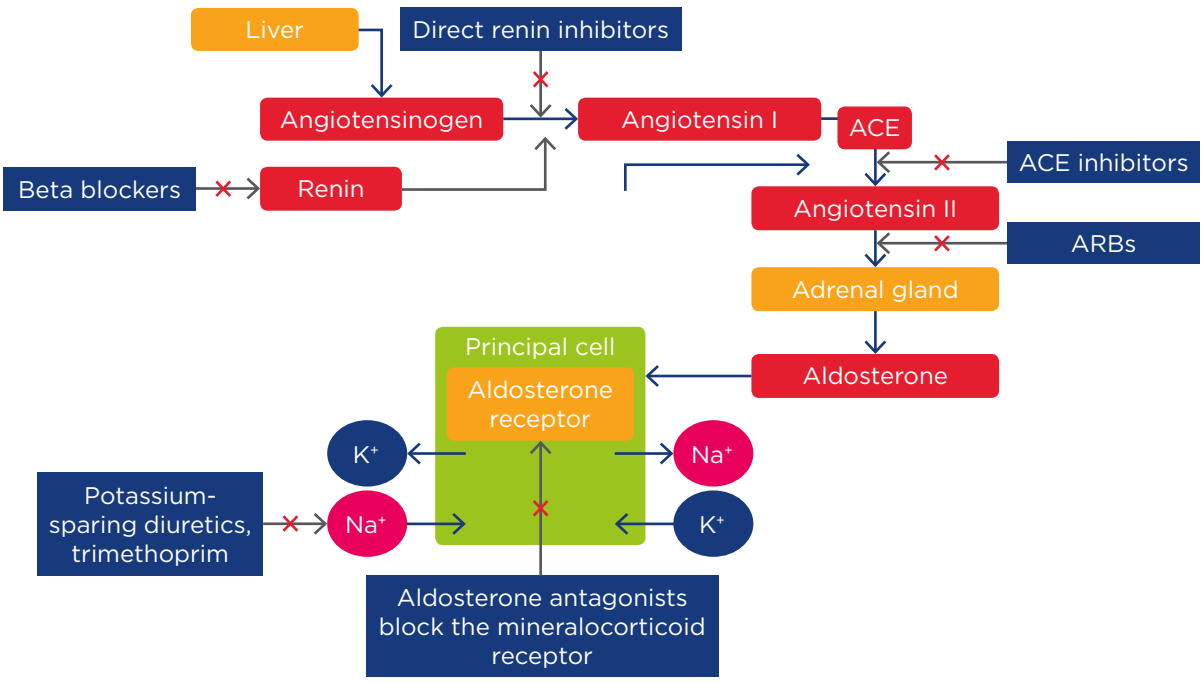

Figure 3: The actions of various renin-angiotensin-aldosterone system inhibitors in causing hyperkalaemia. ACE: angiotensin-converting enzyme; ARBs: angiotensin receptor blockers.

A retrospective analysis of hypertensive patients receiving spironolactone for the treatment of resistant hypertension demonstrated that a 12-fold increase in the rate of patients achieving a satisfactory systolic blood pressure response in a categorical multivariate model was associated with a baseline potassium ion level of <4.5 mEq/L.[26] In hypertensive patients both hyper and hypokalaemia increase mortality risk, as seen from a retrospective analysis of patients included in the Danish National Patient Registry (DNPR) on at least two concomitant antihypertensive drugs (n=44,799).[27]

It is noted that hyperkalaemia can also be caused by other regularly prescribed medications in patients with heart failure and/or hypertension, such as beta blockers and non-steroidal anti-inflammatory drugs, and it is emphasised that alternative hyperkalaemia-reducing agents are required. The actions of various RAAS inhibitors in causing hyperkalaemia are illustrated in Figure 3.

Effect of Hyperkalaemia on Renin-Angiotensin-Aldosterone System Inhibitor Use

Due to the significant risks associated with hyperkalaemia, RAAS inhibitor therapy is often altered following hyperkalaemia events, such as maximum doses being downtitrated to a submaximum dose or even discontinuation of the drugs. In turn, this may lead to greater risk of heart failure readmissions and cardiovascular mortality. In comparison, using the maximum RAAS inhibitor dose is associated with a reduced risk of heart failure hospitalisations and cardiovascular death.[3] Indeed, hyperkalaemia is a key reason for both not starting and discontinuing RAAS inhibitors. In a retrospective review of patients with Stage 3–5 chronic kidney disease, past or current hyperkalaemia was the reason for not starting RAAS inhibitor therapy in 14% of patients, and the reason for discontinuation of RAAS inhibitors in 67% of patients.[28] In the 3-year study using the data from the Geisinger Health System, USA of approximately 200,000 patients, both dose reduction and discontinuation were common in patients with a serum potassium concentration of >5.5 mEq/L receiving ACE inhibitors or angiotensin receptor blockers (n=1,715).[23]

Treatment discontinuation or administration of submaximal doses is a suboptimal approach to managing patients with hyperkalaemia. An alternative approach to hyperkalaemia would allow RAAS inhibitors to be used at their maximum dose and consequently reduce the risk of adverse outcomes from both progressive heart failure and hyperkalaemia.

Currently Available Treatments and Their Limitations

Since the incidence of hyperkalaemia is on the rise due in part to the increase in chronic kidney disease, heart failure, and diabetes as well as greater use of RAAS inhibitors in patients that have clear indications for these therapies (those with heart failure, chronic kidney disease, and/or diabetes), its recognition and treatment is becoming more important than ever.[25,29,30] Unfortunately, current hyperkalaemia treatments have several important limitations so the need for new treatment options is becoming more apparent. The only treatment options currently available are temporising agents such as intravenous calcium, alkalinisation agents (such as sodium bicarbonate), glucose and insulin, and loop diuretics. Calcium is used to stabilise the cardiomyocyte membrane, reducing the risk of conduction abnormalities and cardiac arrhythmias in the setting of hyperkalaemia, but does not directly impact potassium concentrations; in addition, it is only effective over a short time period. Sodium bicarbonate and insulin/glucose act quickly (within approximately 5 minutes) to reduce potassium concentration, and so are useful in times of emergency and can be life-saving. However, these agents do not eliminate excess potassium, and effects are not long-lasting. Both calcium and alkalinisation are usually only effective for 30 minutes, whereas glucose and insulin are effective for ~2 hours. Loop diuretics, on the other hand, have a slower onset of effect, taking 20–60 minutes to reduce potassium concentration, and may not be effective in patients with severely impaired renal function; hence these agents are less useful in the case of an emergency.

Sodium polystyrene sulfonate (SPS) has previously been the only treatment that could be used in addition to loop diuretics to eliminate potassium from the body; it is primarily used in a hospital setting. However, SPS is only weakly selective for potassium, and in fact is more selective for calcium

and magnesium than for potassium.[31] Therefore, the only parts of the gastrointestinal tract where there is a high enough concentration of potassium to be bound by SPS is in the distal colon and rectum. It takes a long time for SPS to reach the distal colon and, hence, the onset of action of SPS to bind and remove potassium is slow.[32]

No well-designed clinical trials have been conducted to prove the efficacy of SPS in lowering potassium levels, since the agent was approved before there was a US Food and Drug Administration (FDA) requirement to demonstrate efficacy and safety in large randomised clinical trials. Furthermore, several small studies suggest that sorbitol, rather than SPS, may be responsible at least in part for the potassium-lowering effect. For example, one study compared the total soluble potassium ions in stools following treatment with a combination of sorbitol and SPS. The levels of total soluble potassium with sorbitol and SPS combined was similar to the results with sorbitol alone.[33]

Some safety concerns also exist with a combination of sorbitol and SPS, such as gastrointestinal tolerability issues. Diarrhoea and constipation are common, particularly with chronic use, as well as in hospital and intensive care units. Furthermore, a FDA alert was released in 2009 highlighting reported cases of colon necrosis, possibly caused by SPS crystals following their administration with sorbitol. The recommendation from this alert was to not co-administer SPS and sorbitol; however, this recommendation has proved difficult to follow as most of the SPS prescriptions in the USA are in combination with sorbitol.[34] The safety issues and lack of efficacy data for SPS as well as the limitations of temporising agents therefore emphasise the clinical need for new hyperkalaemia treatments that are effective and well tolerated.

Novel Treatment Strategies to Manage Potassium Levels

Two novel agents to treat hyperkalaemia have recently emerged: patiromer and SZC. Patiromer is now approved in the USA; it has been studied in several clinical trials to demonstrate its long-term efficacy at lowering potassium and maintaining normal potassium levels for ≤1 year. The mechanism of action of patiromer is non-specific cation binding in exchange for calcium in the distal colon, reducing potassium levels by ~0.2 mEq/L 7 hours after the first dose, and achieving acceptable potassium levels within several days.[35,36]

A randomised blinded trial tested the efficacy of patiromer compared with placebo in patients with mild and moderate-to-severe hyperkalaemia over 4 weeks. Results from the study found that patiromer was superior to placebo, and effectively controlled potassium levels for ≤4 weeks.[35] Patiromer was subsequently studied for ≤1 year in an open-label single-arm study; the results showed that patiromer could be effective at keeping potassium levels controlled over a sustained period of time. Patiromer has been shown to be well tolerated, but hypomagnesaemia and gastrointestinal side effects, such as mild-to-moderate constipation, have been observed.[37]

SZC is another novel potassium binder and is currently in development. SZC is an inorganic crystalline zirconium silicate compound that is insoluble, highly stable, does not expand in water, is not systemically absorbed, and is highly selective for potassium.[38] The mechanism of action of SZC is through selective potassium binding in exchange for sodium and hydrogen, which appears to occur both in the upper and lower gastrointestinal tract based on its rapid onset of action. SZC has been evaluated in one Phase II and two Phase III randomised clinical trials in >1,000 patients. There is also an ongoing ZS005 open-label safety study evaluating SZC in 750 patients for ≤12 months.[39] Studies have shown that SZC normalised potassium levels in 84% of patients by 24 hours (and 98% of patients by 48 hours), and the median time to potassium normalisation was 2.2 hours;[40] the agent was also highly effective in rapidly reducing potassium levels even among patients with severe hyperkalaemia (potassium levels ≥6.0 mEq/L).[41] SZC is well tolerated, but cases of oedema have been observed at high doses.[42]

These novel agents may therefore contribute to a paradigm shift in the management of hyperkalaemia caused by RAAS inhibitors, by optimising serum potassium concentration in the long-term and enabling optimisation of RAAS inhibitor use (and dose) in patients previously ineligible for these treatments. The optimal ways in which these agents may be incorporated into clinical practice among patients with heart failure and resistant hypertension, and their impact on optimisation of RAAS inhibition and ultimately patient outcomes, remains to be established.

New Agents: Unanswered Questions and Clinical Implications

Patiromer and SZC have been studied primarily in outpatients with hyperkalaemia and not in hospitalised patients. Therefore, their effectiveness and safety in the hospital or emergency settings has not yet been evaluated. There are several other important patient groups in which the use of these novel agents should be studied, including those with end-stage renal disease receiving dialysis. Additional clinical trials are also needed to better document the degree with which these agents can optimise RAAS inhibitor use (and dose) in patients with heart failure and reduced systolic function that are unable to tolerate RAAS inhibitor therapy due to previously documented hyperkalaemia, considered to be at high risk for development of hyperkalaemia, or have contraindications to RAAS inhibitor therapy due to potassium levels >5.5 mEq/L or severe chronic kidney disease.

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EDITOR'S PICK

A topic much discussed within global news, the incidence of whiplash claims has rocketed exponentially over the last decade. However, the severity of whiplash injury for affected individuals remains a cause for concern and should not be overlooked by clinicians, regardless of the circumstances. Ling and Sanjay collate the literature published on ocular damage from 1985–2015 and provide a comprehensive example of the extent to which whiplash can harm an individual, highlighting the importance of a thorough patient evaluation to avoid overlooking ophthalmic indicators of hidden damage that may quickly develop into permanent problems.

OCULAR MANIFESTATIONS OF WHIPLASH INJURY

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ABSTRACT

Introduction: Whiplash or indirect injuries to the neck are a common occurrence because of motor vehicle collisions, in which the frequency of ocular complications is largely unknown.

Aim: We aim to review the ocular manifestations, the utility of relevant diagnostic tests, the management, prognosis, and sequelae of whiplash-related ocular complications.

Methods: A comprehensive literature search was conducted on Medline®, PubMed®, Google Scholar™, and Cochrane databases. Only articles published or translated into the English language from 1985–2015 were considered and key data from the full article of each paper were extracted and evaluated.

Results: The authors' search yielded 41 articles. Blurring of vision was the most common presenting symptom. Other common presenting symptoms included words and objects moving within the visual field as well as difficulty in concentration. Ocular findings involved: disturbed eye movements; vestibulo-ocular reflex and cervico-ocular reflex dysfunction; anterior segment abnormalities such as accommodative and convergence dysfunction and relative afferent papillary defect; and posterior segment abnormalities such as macular oedema and foveal lesions. The treatment for ophthalmic complications of whiplash injuries is mainly conservative and revolves around neck physiotherapy and oculomotor rehabilitation. The prognosis of the ocular injury depends on the ocular findings as well as the interval between whiplash injury and treatment initiation.

Conclusion: Whiplash injuries occur commonly in motor vehicle accidents. While patients may present asymptomatically, a myriad of ophthalmic complications may be detected. Prognosis for ocular complications depends mainly on the severity of complication(s), the time lapse between injury and detection of complication(s), and the initiation of treatment. Ophthalmologists and physicians should be aware and vigilant towards patients following whiplash injury as a small minority of patients may have poor visual outcome and quality of life without treatment and follow-up.

Keywords: Whiplash, closed head injury, flexion-extension neck injury, cervical spine injury, ocular, eye, visual.

INTRODUCTION

Whiplash injuries are the most common injuries encountered in motor vehicle accidents. The term 'whiplash' has been described in medical literature as the mechanism in which the head of an occupant is forced backwards with forward recoil, predominantly in a rear-end or side-on collision.[1,2] The acceleration-deceleration transfer of energy to the neck can result in extensive soft tissue and/or bone injury which in turn may lead to a variety of clinical manifestations known as whiplash-associated disorders (WADs). They can be classified by the severity of signs and symptoms into Grades 0–4 according to the Quebec Task Force Classification (QTFC) (Table 1).[3] Patients commonly complain of pain or stiffness in the neck, headache, vertigo, backache, or paraesthesia in the limbs. Although uncommon, ophthalmic and oculomotor complications may also present.

Common ocular manifestations include cervico-ocular reflex (COR) and vestibulo-ocular reflex (VOR) dysfunction, reduced smooth eye pursuit, and nerve palsies. Ocular and oculomotor complications arising from WADs can lead to long-term deficits in visual and systemic functioning. The purpose of this article is to review the commonly reported whiplash-associated ocular complications, their management, prognosis, and sequelae.

MATERIALS AND METHODS

A comprehensive literature search was conducted using Medline®, PubMed®, Google Scholar™, and Cochrane databases using the keywords 'whiplash', 'ocular', 'eye', 'visual', 'closed head injury', 'flexion-extension neck injury', and 'cervical spine injury'. Only studies with abstracts and full-texts published in English from 1985–2015 were included. A hierarchical approach was adopted when selecting articles; relevant articles were initially selected based on their titles and abstracts. The full texts of these articles were then obtained and reviewed in more detail. Articles published before 1985, whiplash injuries because of non-accidental injuries in children, and whiplash injuries associated with penetrating eye injury were excluded from our study to ensure that the mechanism of injury was not confounded by another source. Forty-one studies were eventually collated, comprising 7 observational studies, 1 review article, 21 case series/reports, and 12 case-control studies.

DISCUSSION

Diagnosis of Whiplash Injury

The diagnosis of whiplash injury is made clinically based on the patient's or witness' account of the vehicle accident. Frequently, the mechanism of injury can predict the possibility of a whiplash injury. A high-impact, rear-end, or side-on collision is likely to result in a whiplash injury. The common symptoms of whiplash injury include neck pain, neck stiffness, headache, and memory or concentration disturbances. Radiological investigations usually do not identify abnormalities in the acute setting.[4]

Common Ocular Symptoms of Whiplash Injuries

Ocular symptoms of whiplash injuries may be related to oculomotor control deficits, problems with gaze stability, and head-eye co-ordination disturbances (Table 2). Treleaven and Takasaki[5] compared ocular symptoms reported by individuals with WAD and neck pain, and those with idiopathic neck pain. It was found that individuals with WAD had a higher visual complaints index of mean 32.8±26.0 compared to a visual complaints index mean of 18.8±20.0 in those with idiopathic neck pain.

Table 1: The Quebec Task Force Classification (QTFC) of whiplash-associated disorders.[3]

Grade	Classification
0	No complaint about neck pain and no physical signs
1	Neck complaint of pain, stiffness, or tenderness only, no physical signs
2	Neck complaint and musculoskeletal signs; musculoskeletal signs include a reduced range of movement and point tenderness
3	Neck complaint and neurological signs; neurological signs include decreased or absent deep tendon reflexes, weakness, and sensory deficits
4	Neck complaint and fractures or dislocations

Table 2: Common ocular clinical symptoms and signs associated with whiplash-associated disorders.

Common ocular symptoms
Blurred vision Words or objects moving Needing to concentrate
Common ocular signs
Ocular signs involving eye movements Nerve palsies Superior oblique muscle deficit Internuclear ophthalmoplegia Saccadic eye movement deficits Smooth pursuit deficits
Ocular complications involving the anterior segment of the eye Hyphema Traumatic mydriasis Accommodative and convergence dysfunction Relative afferent papillary defect Horner's syndrome Increased intraocular pressure
Ocular complications involving the posterior segment of the eye Macular oedema Foveal lesions Ocular haemorrhages Commotio retinae Macular detachment Optic disc oedema Retinal detachment Retinoschisis Foveomacular retinitis Retinal epithelial tears
Vestibulo-ocular reflex and cervico-ocular reflex dysfunction

Individuals with WAD also had a significantly greater magnitude of complaints of blurred vision compared to individuals with idiopathic neck pain (55% versus 32%), words or objects moving (48% versus 24%), and needing to concentrate (72% versus 60%). Other symptoms include visual fatigue, sensitivity to light, double vision, difficulty judging distance, red eyes, and dizzy reading. The report also confirmed that double vision and red eyes did not appear to be associated with neck pain as there were no differences in reported prevalence and magnitude of these symptoms in subjects with neck pain when compared to asymptomatic individuals. Burke et al.[6] also reported three cases of decreased stereoacuity, of which two were asymptomatic. These symptoms can greatly impact the quality of life of individuals.

Ocular Complications Involving Eye Movements

Nerve palsies

Out of the 41 articles, 13 documented cranial nerve palsies, especially those that control the eye movement, namely the oculomotor (CN3), trochlear (CN4), and abducens (CN6) nerves. Abducens nerve palsy was the most common injury sustained, as described in 13 articles.[7-19] One retrospective study[7] identified 17 (28.3%) cases of CN3 and 20 (33.3%) cases of CN4 palsies in the 60 cases examined. Additionally, combined nerve palsies constituted five cases (8.3%). In the 13 articles, bilateral abducens palsies were present in 12 patients,[8,9,11-15,17-19] unilateral left abducens palsy occurred in 1 patient[10] while the rest were unspecified.[7,10,16] The abducens nerve is most commonly involved as it runs a long intracranial course and is vulnerable to injury. It can be injured at the following areas during its course:[10]

- As it crosses the petrous part of the temporal bone
- Stretched as it passes from the brainstem to its entry to the dura at the basilar process by downward and forward displacement of the brainstem during whiplash injury
- Fracture of the cranial floor
- Meningeal oedema
- Inflammation within the skull base

Delayed presentation of abducens nerve palsy was reported in two papers[17,18] with an interval of 3 days to 6 weeks. Delayed presentations have been postulated to be because of vasospasm or injury to branches of the meningodorsal artery causing nerve ischaemia.[20] The other cause could be due to surrounding tissue oedema, a mechanism akin to delayed traumatic facial palsy.[21] Associated injuries to the cervical spine, diagnosed using imaging studies, were also reported in six cases.[8,13-15,18] Abducens nerve palsy can also relay false localising signs due to raised intracranial pressure. In the 13 articles studied, raised intracranial pressure causing bilateral abducens palsy was only suggested in one patient,[17] with the majority reporting unremarkable computed tomography (CT) brain findings. Of the 79 cases of nerve palsies reported, 67 reported diplopia while the rest were asymptomatic or had unspecified ocular symptoms.

Other cranial nerve involvement

One article documented the presence of unilateral hypoglossal nerve palsy.[19] Steroids were used as treatment in three cases with isolated bilateral abducens palsy. Of these three cases, one resolved completely, one resolved partially, and one remained persistent after 1 year, 6 months, and 3 months, respectively. Six cases received treatment for associated cervical spine injury, all of which had abducens palsy that resolved. Others had no treatment or treatment that was unspecified.

Only 12 patients[8-15,17-19] were reported to be on regular follow-up, with the duration of follow-up ranging from 3 months to 1 year post-injury (mean: 6.5 months). Of these 12 patients, 7 had abducens palsy completely resolved (mean follow-up: 7.3 months), 3 had abducens palsy partially resolved (mean follow-up: 7 months), and 2 patients did not improve over time (mean follow-up: 3 months). Mutyala et al.[22] reported a spontaneous improvement rate of 27% in unilateral traumatic sixth-nerve palsy and 12% in bilateral traumatic sixth-nerve palsy. However, Holmes et al.[23] reported an overall spontaneous recovery rate of 73%. Spontaneous recovery was more frequent in unilateral cases (84%) than in bilateral cases (38%).[7]

Extraocular Muscle Involvement

Burke at al.[6] described three cases of superior oblique muscle involvement. Two cases had superior oblique muscle paresis while one case had an underaction of the superior oblique muscle. The latter case was also described to have other ocular signs such as hypometric horizontal saccades, a reduction in convergence, and cogwheel pursuits. The aetiology of the cases is uncertain but has been suggested to be because of axonal shearing of the trochlear nerve and stretching forces at the moment of impact. All three cases recovered within 1 year of the accident.

Other Ocular Complications

Jammes[24] reported a case of internuclear ophthalmoplegia occurring immediately following a whiplash injury in a 58-year-old lady. Extensive recovery was achieved after a 1-year follow-up.

Oculomotor Dysfunction

Deficits in saccadic eye movements and smooth pursuit eye movements were noted.[25-34] Electro-oculography, electronystagmography, and a smooth pursuit neck torsion test were some of the common investigations conducted to detect the deficits. Storaci et al.[25] reported that oculomotor rehabilitation conducted within 3 months of injury could help to improve pursuit eye movement deficits. Kongsted et al.[33] suggested that other symptoms, such as persistent neck pain, could help to predict prognostic outcome of oculomotor dysfunction. Persistent neck pain was found to be associated with reduced smooth pursuit performance at 1-year follow-up.

Ocular Complications Involving the Anterior Segment of the Eye

Hyphema and traumatic mydriasis

Mustafa et al.[35] in their case report accounted for the presence of hyphaema in a 25-year-old gentleman who presented with a visual acuity of light perception. Visual acuity improved to counting fingers after 4 months. The gentleman also presented with extensive commotio retinae with associated gross macular detachment, fine vitreous haemorrhage, and traumatic mydriasis.

Pupillary dysfunction

Stimulation to the sympathetic pathway due to injury to the cervical neck can result in pupillary dysfunction. Relative afferent papillary defect was also described in one case by Williams et al.[36] Accommodation and convergence dysfunction were described in 19 and 10 cases respectively by Burke et al.[6] and Brown.[37]

Horner's syndrome

Horner's syndrome was noted in two case reports. Uzan et al.[8] accounted for the presence of a left Horner's syndrome associated with bilateral abducens nerve palsy in a 42-year-old gentleman. Jammes[24] presented a case of right Horner's syndrome in a 58-year-old lady who also suffered bilateral internuclear ophthalmoplegia. Due to the relationship between the anatomy of structures of the neck and the cervical sympathetic trunk, any injury to the cervical region following a whiplash mechanism can account for Horner's syndrome.

Increased intraocular pressure

Wei and Spaeth[38] accounted for four cases of transient increase in intraocular pressure in patients with an established background of open angle glaucoma. Intraocular pressure increased by the range of 5–19 mmHg. All four patients required an increase in dosage of topical medication or an additional topical medication. Intraocular pressure decreased to pre-accident levels in all cases within 1 year of the accident.

Ocular Complications Involving the Posterior Segment of the Eye

Complications involving the posterior segment of the eye may be attributed to shearing stresses generated from the acceleration-deceleration forces, raised intracranial and intraocular pressures, and the breakdown in the blood-retinal barrier.

Macular oedema

Macular oedema has been described immediately after whiplash injury.[39,40] The swelling can be symptomatic and persistent at 6-month follow-up sessions[39] or resolve completely after 1 year.[40]

Foveal lesions

Foveal lesions, which include perifoveal lesions with paracentral scotoma, have been described immediately following a whiplash injury. The effectiveness of optical CT to detect lesions at the vitreoretinal interface related to whiplash maculopathy has been emphasised.[39] Small yellowish lesions over the fovea with loss of normal foveal reflex were found in fundoscopy on a patient who had complained of decreased central vision 1 year after a whiplash injury.[41] There were also persistent signs and symptoms at 6 months and 20 months later. Williams et al.[36] described swelling of the foveal zone and a foveal pit. It is proposed that the foveolar pit is due to selective destruction of the central photoreceptors, which may occur secondary to physical or toxic agents, and that no treatment had been proven effective.

Other posterior segment complications

Other less common posterior segment complications include vitreous detachment,[6] vitreous haemorrhages,[35] commotio retinae,[35] macular detachment,[35] Terson syndrome (vitreous haemorrhage associated with subarachnoid haemorrhage),[36] optic disc oedema,[36] relative afferent papillary defect,[36] retinal detachment,[42] retinoschisis,[42] foveomacular retinitis,[43] dot-blot haemorrhages,[44] and retinal epithelial tears.[45]

Vestibulo-ocular reflex and cervico-ocular reflex dysfunction

The COR works with the VOR and optokinetic reflexes to control the extra-ocular muscles creating clear vision with head movement.[46,47] Damaged cervical afferent input, both proprioceptive and nociceptive, from injury to the cervical region or injury to the brainstem during a whiplash injury can result in deficits. Neck pain resulting in restricted neck movements has also been described to affect oculomotor performance.[30] Four articles[48-51] have described VOR and COR dysfunction, specifically an increased gain in COR. Bexander and Hodges[48] also reported a decreased co-ordination between the COR and VOR. VOR and COR can be evaluated using electro-oculography.

Ocular Complications Due to Similar Mechanisms of Head Injury

In extrapolation, we have found ocular injuries due to a similar mechanism of head injury, specifically bungee jumping. Ocular injuries due to bungee jumping have been reported in several case reports. The most common ocular symptom is blurring of vision[52-54] which spontaneously resolves after a few weeks. Common ocular signs include subconjunctival haemorrhage,[52-54] periorbital bruising,[53] and retinal haemorrhages.[53,54] Less common but reported symptoms include horizontal diplopia,[54] nystagmoid jerks on versions,[54] vitreous haemorrhage,[53,54] retinal detachment,[52] and macular oedema.[53,54]

The mechanism of injury has been postulated to be because of the rise in intrathoracic pressure during the sudden deceleration phase of the jump, consequently increasing intravenous pressure

and hydrostatic pressure in the intraocular circulation.[52-54] Breath holding and tensing of the abdominal muscles during the jump are also contributors to the increase in intrathoracic pressure.[52,54] A gravitational force of -3.0 G has been shown to be sufficient to cause ocular injuries.[52-54]

Treatment

The treatment of ocular complications of whiplash injury should be based on the deficits identified during physical examination and investigation outcomes. Commonly, treatment is conservative and revolves around neck physiotherapy and oculomotor rehabilitation, which involves oculomotor convergence and motility exercises. Early rehabilitation can predict a better outcome. Controlling pain and inflammation may also help to improve outcomes.

CONCLUSION

Whiplash injuries occur commonly in motor vehicle accidents. While patients may present asymptomatically, a myriad of ocular complications may be detected. This possibly highlights the need for ophthalmologists and physicians to conduct basic ophthalmological examinations for all patients who present with whiplash injury. Prognosis for ocular complications depends mainly on the severity of complication and the time lapse between injury, detection of complication, and initiation of treatment. Ophthalmologists and physicians should be aware and vigilant towards patients with ophthalmic complaints following whiplash injury as a small minority of patients may have poor visual outcome and increased morbidity without treatment and follow-up.

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RECENT DEVELOPMENTS IN REGORAFENIB TREATMENT FOR GASTROINTESTINAL CANCERS: PRESENTATIONS AT THE EUROPEAN SOCIETY FOR MEDICAL ONCOLOGY (ESMO) CONGRESS 2016

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ABSTRACT

The European Society for Medical Oncology (ESMO) Congress was held in Copenhagen, Denmark from 7th–11th October 2016. The use of the promiscuous multikinase inhibitor regorafenib (Stivarga®, BAY 73-4506) in the treatment of cancers of the gastrointestinal (GI) tract was strongly featured at this meeting. Regorafenib targets multiple kinases involved in oncogenesis and angiogenesis, and is US Food and Drug Administration (FDA)-approved for the treatment of advanced metastatic colorectal cancer and GI stromal tumours, following progression on standard therapies. In this review, we summarise the results of completed clinical trials on the use of regorafenib alone or in combination with other therapies for the treatment of GI cancers. We highlight the results of the Phase III RESORCE study which demonstrated the efficacy of regorafenib as a second-line therapy in patients with advanced hepatocellular carcinoma who have progressed on sorafenib. We review some promising preliminary data on the use of regorafenib in other GI cancers, such as gastric cancer, oesophageal cancer, pancreatic cancer, and soft tissue carcinomas, and provide a brief overview of ongoing and planned trials. Finally, we discuss the incidence and management of regorafenib-related toxicities and summarise attempts to identify predictive biomarkers of regorafenib sensitivity.

Keywords: Colorectal cancer (CRC), gastric cancer (GC), gastrointestinal stromal tumours (GISTs), hepatocellular carcinoma (HCC), tyrosine kinase inhibitor.

INTRODUCTION

The term gastrointestinal (GI) cancer refers to all tumours affecting the digestive tract, including gastric cancer (GC), colorectal cancer (CRC), oesophageal cancer, pancreatic cancer, cholangiocarcinoma (CCC), hepatocellular carcinoma (HCC), and sarcomas such as GI stromal tumours (GISTs). CRC was one of the most frequently diagnosed GI malignancies within Europe in 2012, with a reported incidence of 446.8 per 100,000, followed by GC (139.6 per 100,000), and HCC (63.4 per 100,000).[1] The precise incidence of GISTs remains unknown, although it is estimated to comprise <1% of all GI cancers.[2] Recommended treatment varies depending on the type of GI tumour. Radical surgery is the mainstay treatment for all GI cancers; however, many patients will develop recurrent or metastatic disease: in most cases, the disease is deemed incurable. In this setting, targeted anti-angiogenic therapies, such as monoclonal antibodies targeting vascular

endothelial growth factor (VEGF) have attracted attention. Despite the success of these targeted therapies (summarised in Table 1),[3] primary and secondary resistance remains a clinical challenge, with clonal evolution of resistant cells leading to the need for additional lines of therapy. Following the development of resistance, tyrosine kinase inhibitors or multikinase inhibitors (MKIs) may present an effective option in the clinic, likely due to their broad substrate specificity.

Regorafenib (Stivarga®, BAY 73-4506) is a promiscuous MKI that is US Food and Drug Administration (FDA)-approved for the treatment of advanced metastatic CRC (mCRC) and GISTs following progression on standard therapies. However, despite its proven efficacy, regorafenib is associated with a number of treatment-related toxicities. Presentations at the European Society for Medical Oncology (ESMO) Congress 2016 reflected the continuing efforts to refine the regorafenib treatment regimens and manage treatment-related toxicities. In this review, we illustrate the recent advances in clinical trial data regarding regorafenib alone or in combination with other therapies for the treatment of GI cancers, provide an overview of some ongoing and planned trials, and discuss options for managing regorafenib-related toxicities.

REGORAFENIB AS AN ANTI-TUMOUR AGENT

Regorafenib demonstrates anti-tumour activity in a variety of *in vitro* and *in vivo* models.[4,5] It acts on several protein kinases involved in important aspects of tumour growth, including angiogenesis (VEGF receptors [VEGFRs] 1–3 and TIE2), oncogenesis (KIT, RET, RAF1, B-RAF, and B-RAF-V600E), and the tumour microenvironment (platelet-derived growth factor receptor [PDGFR] and fibroblast growth factor receptor [FGFR]).[4] Regorafenib also targets apoptosis-related pathways (e.g. SHP-1 and PUMA).[6,7] It was recently shown to display anti-angiogenic, anti-proliferative, and pro-apoptotic activity in patient-derived murine models of GC.[5] Regorafenib first demonstrated clinical activity in a Phase I trial in heavily pretreated mCRC patients,[8] and has since shown promising efficacy and tolerability for the treatment of various GI cancers in a number of Phase II and Phase III clinical trials (Table 2).

REGORAFENIB AND METASTATIC COLORECTAL CANCER

Regorafenib therapy demonstrated significant improvements in terms of overall survival (OS, primary endpoint), progression-free survival (PFS), and disease control (DCR) in heavily pretreated mCRC patients in two placebo-controlled, randomised, Phase III trials: CORRECT (NCT01103323, N=753) and CONCUR (NCT01584830, N=204) (Table 2).[9,10] In CONCUR, median OS was 8.8 versus 6.3 months for placebo (hazard ratio [HR]: 0.55; 95% confidence interval [CI]: 0.40–0.77; p=0.0002), whereas median OS was 6.4 versus 5 months for placebo in CORRECT (HR: 0.77; 95% CI: 0.64–0.94; p=0.0052).[9,10] The longer OS observed in the CONCUR trial may reflect the fact that patients were not as heavily pretreated: 38% of patients in the regorafenib arm in CONCUR were treated with ≥4 lines of prior therapy versus 49% in CORRECT.[9,10] In CORRECT, all patients were pretreated with anti-VEGF therapies and ~50% (all *KRAS* wild-type cancers) were pretreated with an anti-epidermal growth factor receptor (EGFR), whereas in CONCUR, only ~60% were pretreated with either of these therapies (40% were not pretreated with any targeted therapy).[9,10] The sample size was also smaller in the CONCUR trial. Another difference is that all patients in CONCUR were of Asian descent compared to only 15% of patients in CORRECT. The most frequent regorafenib-related adverse events (AEs) (Grade ≥3) in the CORRECT trial were hand-foot-skin reaction (HFSR; 17%), fatigue (10%), diarrhoea (7%), and hypertension (7%);[9] in CONCUR, they were HFSR (16%), hypertension (11%), hyperbilirubinaemia (7%), hypophosphatemia (7%), and alanine aminotransferase increase (7%).[11]

Similar efficacy and safety results were observed in two open-label, single-arm studies performed in real-world settings: REBECCA (NCT02310477) and CONSIGN (NCT01538680) (Table 2).[12-14] REBECCA, a French compassionate programme, was a cohort study designed to evaluate the efficacy and safety of regorafenib in pretreated mCRC patients in real-life clinical practice. All patients (N=654) included in REBECCA received regorafenib, resulting in a median OS of 5.6 months and a 12-month survival rate of 22%.[12,13] Fatigue and HFSR were the most common AEs (Grade ≥3).[12,13] The open-label, single-arm, Phase IIIb CONSIGN study (N=2,872) conducted across 25 countries was designed to further characterise the safety of regorafenib

in mCRC patients who had failed standard therapy.[14,15] In CONSIGN, regorafenib-related AEs (all grades) were observed in 91% of patients.[14,15] It was proposed that elderly patients may be at increased risk of these toxicities; however, subgroup analysis of the CONSIGN study population based on age showed that regorafenib-related AEs were generally comparable in patients aged <65 and ≥65 years, with both subgroups showing similar PFS (~2.5 months).[16]

Regorafenib has been examined as a first-line therapy in mCRC patients who were frail or unfit for polychemotherapy (due to various comorbidities) in the Phase II REFRAME trial (NCT01875380), an ongoing open-label single-arm study with a primary outcome measure of PFS.[17] Preliminary safety data from REFRAME on 44 patients revealed that 9 patients discontinued treatment due to regorafenib-related toxicity or death;[18] however, there remains insufficient data regarding the efficacy of regorafenib in this setting.

Regorafenib as a first or second-line treatment for mCRC in combination with chemotherapy (FOLFIRI or irinotecan, 5-fluorouracil, and leucovorin) was examined in a Phase Ib multicentre, randomised, placebo-controlled study.[19] Of the 45 patients undergoing the combined therapy, 33 achieved DCR (partial response or stable disease) for a median of 126 (range: 42–281) days.[19] Treatment was stopped in 17 patients due to regorafenib-related AEs or death.[19] Regorafenib-related AEs (Grade ≥3) occurred in 32 patients, mostly neutropenia (53%), leukopenia (12.5%), HFSR (12.5%), and hypophosphatemia (12.5%).[19] Subsequently, a Phase II study confirmed that the addition of regorafenib on an intermittent schedule to FOLFIRI was tolerable and resulted in a statistically significant prolongation of PFS compared to FOLFIRI alone (Table 2).[20] While regorafenib plus FOLFIRI treatment also improved OS in this study, the difference was not statistically significant.[20] However, whether subsequent therapies or crossover influences the OS in this population remains under investigation.

Ongoing trials include the prospective cohort CORRELATE trial (N≥1,000, NCT02042144) on the safety of regorafenib for mCRC therapy in routine clinical practice[21] and the open-label Phase II REGARD trial (NCT01853319) enrolling 100 Turkish mCRC patients with progression after standard therapy with fluoropyrimidine, oxaliplatin, irinotecan, bevacizumab, and an EGFR inhibitor (if the patient is *KRAS* wild-type).[22,23]

Table 1: Examples of currently available targeted therapies for gastrointestinal cancers approved by the European Medicines Agency (EMA) or US Food and Drug Administration (FDA).

Name	Target(s)	Indication
Bevacizumab	mAb (targets VEGF-A)	Metastatic colorectal cancer
Aflibercept	VEGFR decoy receptor	Metastatic colorectal cancer
Ramucirumab	mAb (targets VEGF-binding domain of VEGFR-2)	Metastatic gastric cancer, metastatic colorectal cancer, metastatic gastro-oesophageal junction adenocarcinoma, oesophageal cancer
Cetuximab	mAb (targets EGFR)	Metastatic colorectal cancer
Panitumumab	mAb (targets EGFR)	Metastatic colorectal cancer
Trastuzumab	mAb (targets HER2)	HER2-overexpressing metastatic gastric cancer or gastro-oesophageal junction adenocarcinoma
Sorafenib	Multitarget TKI	Advanced hepatocellular carcinoma
Imatinib	Multitarget TKI	Gastrointestinal stromal tumours
Sunitinib	Multitarget TKI	Imatinib-resistant gastrointestinal stromal tumours
Regorafenib	Multitarget TKI (targets VEGFR1–3, c-KIT, TIE-2, PDGFR-β, FGFR-1, RET, RAF-1, B-RAF, and p38 MAP kinase)	Metastatic colorectal cancer, advanced gastrointestinal stromal tumours

EGFR: epidermal growth factor receptor; FGRF: fibroblast growth factor receptor; HER2: human epithelial growth factor receptor 2; mAb: monoclonal antibody; PDGFR: platelet-derived growth factor receptor; TKI: tyrosine kinase inhibitor; VEGF: vascular endothelial growth factor; VEGFR: vascular endothelial growth factor receptor.

Table 2: Summary of the results of completed Phase II/III trials on the use of regorafenib in gastrointestinal cancers.

Trial name/ID	Indication	Study design	Study size (N)	Line of therapy	Efficacy outcomes	Safety
CONCUR **Clinical Trial: NCT01103323**[10]	mCRC	Randomised (2:1) Phase III	204	Third or fourth	Improved OS (8.8 versus 6.3 months for placebo; HR: 0.55; 95% CI: 0.40–0.77; p=0.00016).	Treatment-related AEs (all grades) were reported in 97% of patients. Most common treatment-related AEs (Grade ≥3) were HFSR (16%) and hypertension (11%).
CORRECT **Clinical Trial: NCT01103323**[9]	mCRC	Randomised (2:1) Phase III	753	Third or fourth	Improved OS (6.4 versus 5.0 months for placebo; HR: 0.77; 95% CI: 0.64–0.94; p=0.0052).	Treatment-related AEs (all grades) were reported in 93% of patients. Most common treatment-related AEs (Grade ≥3) were HFSR (17%) and fatigue (10%).
CONSIGN **Clinical Trial: NCT01538680**[14,15]	mCRC	Expanded access Phase IIIb	2,872	Third or fourth	Median PFS (95% CI) was 2.7 months (2.6–2.7).	Treatment-related AEs (all grade) were reported in 91% of patients. Most common treatment-related AEs (Grade ≥3) were HFSR (57%), fatigue (15%), diarrhoea (14%), and hypophosphatemia (13%).
REBECCA **Clinical Trial: NCT02310477**[12,13]	mCRC	Open-label single arm, real-life, observational	654	Second or third	Median OS of 5.6 months and 12-month survival rate of 22%.	Treatment-related AEs (all grades) were reported in 80% of patients. Most common treatment-related AEs (Grade ≥3) were fatigue (15%), HFSR (9%), and diarrhoea (4%).
REG+FOLFIRI **Clinical Trial: NCT01289821/ NCT01298570**[19]	mCRC	Randomised (2:1) Phase II efficacy	45	First or second (after FOLFOX regimen)	DCR achieved in 73% of patients for a median of 126 days (range, 42–281 days).	Treatment-related AEs were reported in 98% of patients. Most common treatment-related AEs (Grade ≥3) were neutropenia (38%), HFSR (8%), and hypophosphatemia (8%).
REG IN HCC **Clinical Trial: NCT01003015**[24]	HCC	Phase II (safety)	36	Second (after sorafenib)	DCR achieved in 72% of patients. Median OS of 13.8 months.	Most common treatment-related AEs (Grade ≥3) were fatigue (17%), HFSR (14%), diarrhoea (6%), hyperbilirubinemia (6%), and hypophosphatemia (6%).
RESORCE **Clinical Trial: NCT01774344**[25-27]	HCC	Randomised (2:1) Phase III	573	Second (after sorafenib)	Improved OS (10.6 versus 7.8 months in placebo) and PFS (3.1 versus 1.5 months for placebo).	Most common treatment-related AEs (Grade ≥3) were hypertension (15.2%), HFSR (12.6%), fatigue (9.1%), and diarrhoea (3.2%).

Table 2 continued.

Trial name/ID	Indication	Study design	Study size (N)	Line of therapy	Efficacy outcomes	Safety
INTEGRATE **Clinical Trial: ANZCTR 12612000239864**[29]	AOGC	Randomised (2:1) Phase II	152	Second or third	Improved PFS (2.6 versus 0.9 months for placebo; HR: 0.40; 95% CI: 0.28–0.59; p<0.001).	Toxicity generally consistent with the known profile of REG.
REG IN GIST **Clinical Trial: NCT01068769**[34]	GIST	Phase II	33	Second (after imatinib and sunitinib)	Median PFS was 10 months (95% CI: 8.3–14.9).	Most common treatment-related AEs (Grade ≥3) were hypertension (36%) and HFSR (24%).
GRID **Clinical Trial: NCT01271712**[35,48]	GIST	Randomised (2:1) Phase III	199	Second (after imatinib and sunitinib)	Improved PFS (4.8 versus 0.9 months for placebo; HR: 0.27; 95% CI: 0.19–0.39; p<0.0001).	Treatment-related AEs (all grades) were reported in 98% of patients.

AEs: adverse events; AOGC: advanced oesophago-gastric cancer; CI: confidence interval; DCR: disease control; GIST: gastrointestinal stromal tumours; HCC: hepatocellular carcinoma; HFSR: hand-foot-skin reaction; HR: hazard ratio; mCRC: metastatic colorectal cancer; OS: overall survival; PFS: progression-free survival; REG: regorafenib.

REGORAFENIB AND HEPATOCELLULAR CARCINOMA

Sorafenib is the recommended first-line treatment for advanced HCC patients; however, there are no proven or approved second-line treatment options for sorafenib-treated patients who experience disease progression. Therefore, following promising Phase II data,[24] the international, randomised, Phase III, double-blind, placebo-controlled trial RESORCE study (NCT01774344) was initiated to investigate single-agent therapy with regorafenib in patients with intermediate/advanced HCC after progression on sorafenib (Table 2).[25] In RESORCE, patients with HCC Barcelona Clinic Liver Cancer (BCLC) Stage B or C, who had documented radiological progression on sorafenib, Child–Pugh A liver function, and Eastern Cooperative Oncology Group (ECOG) performance status 0–1, were randomised (2:1) to regorafenib (n=379) or placebo (n=194).[26,27] Compared to placebo, regorafenib improved median OS (primary endpoint, 10.6 versus 7.8 months for placebo; HR: 0.62; 95% CI: 0.50–0.78; p<0.001) and PFS (3.1 versus 1.5 for placebo; HR: 0.46; 95% CI: 0.37–0.56; p<0.001).[27] Regorafenib also significantly improved DCR (65.2% versus 36.1% for placebo; p<0.001).[27] The most common regorafenib-related AEs (Grade ≥3) were hypertension (15.2%), HFSR (12.6%), and fatigue (9.1%).[27] Therefore, single-agent regorafenib may fulfil the need to provide effective second-line treatment in advanced HCC patients who have progressed on sorafenib.

REGORAFENIB IN GASTRIC AND OESOPHAGEAL CANCER

Regorafenib has shown anti-tumour activity in patient-derived murine models of GC.[5] While further research is required to confirm its efficacy in GC patients, single-agent regorafenib has shown promising results in the randomised, double-blind, placebo-controlled Phase II INTEGRATE study (ACTRN12612000239864) on refractory advanced oesophago-gastric cancer patients (Table 2).[28] In INTEGRATE, median PFS (primary endpoint) was significantly longer in the regorafenib arm (n=97) than the placebo arm (n=50; 2.6 versus 0.9 months, respectively; HR: 0.40; 95% CI: 0.28–0.59; p<0.001).[29] The effect on PFS was greater in South Korea than in Australia, New Zealand, and Canada combined (HR: 0.12 versus 0.61; interaction p<0.001) but was consistent across age, neutrophil-to-lymphocyte ratio, primary site, lines of chemotherapy, peritoneal metastasis presence, number of metastatic sites, and plasma VEGF-A.[29] Regorafenib treatment

also showed a longer survival trend compared to placebo (although this difference was not statistically significant) and AEs were similar to those previously reported.[29] Following the success of INTEGRATE, a randomised Phase III trial (INTEGRATE II) is currently recruiting participants (ACTRN12616000420448).[30] In addition, regorafenib is currently being investigated in combination with FOLFOX in a randomised Phase II study of patients with unresectable or metastatic, advanced oesophago-gastric cancer (NCT01913639).[31]

REGORAFENIB AND PANCREATIC CANCER

Promising data concerning the use of regorafenib in pancreatic cancer arose from the Phase I, multicentre, single-arm trial that enrolled 15 patients with treatment-refractory solid tumours, in which the most common tumour site was the pancreas.[32] More than half of these patients achieved DCR with regorafenib therapy (partial response, n=1; stable disease, n=7).[32] Regorafenib-related toxicities were mostly mild or moderate, and included HFSR, diarrhoea, hypophosphatemia, and liver transaminase elevation.[32] A Phase II trial comparing regorafenib with gemcitabine in the treatment of metastatic pancreatic cancer is also ongoing (NCT02383433).[33] However, until its safety and efficacy is confirmed, regorafenib must not be used in the treatment of pancreatic cancer outside clinical trial settings.

REGORAFENIB AND SARCOMAS

Regorafenib was FDA-approved as a third-line therapy for patients with metastatic and/or unresectable GIST following results of the Phase II[34] and Phase III (NCT01271712) GRID trials[35] (Table 2). Regorafenib is also under investigation for the treatment of patients with advanced soft tissue sarcomas (STS) in the REGOSARC trial (NCT01900743), which comprises four parallel, double-blind placebo-controlled, randomised Phase II trials defined by four histological subgroups: liposarcoma, leiomyosarcoma, synovial sarcoma, and other sarcomas.[36] In REGOSARC, 182 patients with anthracycline pretreated metastatic STS were randomly assigned to one of the above four cohorts.[37] While liposarcoma patients treated with regorafenib showed no significant difference in median PFS (primary outcome) compared to placebo (1.1 versus 1.7 months, respectively; HR: 0.89; 95% CI: 0.48–1.64; p=0.7), leiomyosarcoma patients treated with regorafenib had significantly longer PFS (3.7 versus 1.8 months for placebo; HR: 0.46; 95% CI: 0.46–0.80; p=0.0045).[37] Similarly, in the synovial sarcoma cohort, the median PFS of patients treated with regorafenib was significantly longer compared to placebo (5.6 versus 1.0 months, respectively; HR: 0.10; 95% CI: 0.03–0.35; p<0.0001).[38] In patients with other types of sarcomas, PFS was also significantly longer in the regorafenib arm compared to placebo (2.9 versus 1.0 months, respectively; HR: 0.46; 95% CI: 0.25–0.81; p=0.0061).[38] Therefore, further clinical evaluation of regorafenib in patients with sarcomas is warranted.

REGORAFENIB IN OTHER CANCERS

Regorafenib is currently undergoing numerous Phase II clinical trials for cancers beyond the GI tract, including the randomised REGOBONE trial (NCT02389244) on the efficacy and safety of regorafenib in the treatment of metastatic bone sarcomas.[39] Recruitment is also ongoing for a Phase II trial on single-agent regorafenib in patients with advanced and metastatic biliary tract carcinoma/CCC who have failed first-line chemotherapy (NCT02053376),[40] as well as the Phase II randomised REACHIN trial for CCC (NCT02162914).[41] Although the final analysis is yet to be completed, a Phase II study for the treatment of progressive, recurrent/metastatic adenoid cystic carcinoma was recently reported to have failed to meet its primary endpoints.[42] Finally, a Phase I study (NCT02466802) on the combined use of regorafenib and sildenafil citrate (an inhibitor of phosphodiesterase Type 5 that potentiates anti-cancer activity)[43] in the treatment of advanced solid tumours is currently recruiting participants.[44]

PREDICTIVE BIOMARKERS OF THE REGORAFENIB RESPONSE

While biomarkers have been extensively investigated in randomised trials, we are yet to identify a single factor predictive of regorafenib sensivitiy.[45] Indeed, preliminary analysis of genetic prognostic and predictive factors in the REGOSARC study showed that none of the individual genes encoding regorafenib-targeted proteins (i.e. *VEGFR1–3*, *FGFR1*, *KIT*, *PDGFRB*, *RAF1*, *RET1*, *TIE2*, *TP53*, and *CHP2*) were predictive of response or PFS in STS patients, although further combinatorial analyses are ongoing.[46] In GIST patients, regorafenib treatment suppressed plasma

nitric oxide levels and increased endothelin-1 levels,[47] indicating they are potential biomarkers. Regorafenib also showed a particular benefit among GIST patients with primary *KIT* exon 11 mutations and those with succinate dehydrogenase-deficient GIST.[48] In pancreatic cancer, PD-L1^{+}/PD-1^{+} patients may have improved benefit from regorafenib.[49]

For mCRC patients, post hoc subgroup analyses of the CORRECT and CONSIGN study populations according to PFS revealed that patients with long PFS (>4 months) tended to have better performance status, fewer metastatic tumour sites, and a longer time since diagnosis of metastatic disease compared to those with short PFS (≤4 months).[50,51] However, a prospective validation of this data is needed to draw further conclusions. Similarly, subgroup analysis of the REBECCA trial data revealed that survival was independently and unfavourably affected by poor performance status, short time from initial diagnosis of metastases to the start of regorafenib, low initial regorafenib dose, >3 metastatic sites, presence of liver metastases, and *KRAS* mutations.[12,13] These data suggest that mCRC patients could be classified into prognostic groups by collecting simple baseline characteristics and or mutational status. Indeed, retrospective analysis of the CORRECT trial data indicated that *KRAS* and *PIK3CA* mutational status and circulating DNA concentration are potentially associated with clinical benefit from regorafenib.[52]

Imaging techniques may also prove useful in this area, with contrast-enhanced computed tomography (CT) texture reported as a potential biomarker for response to tyrosine kinase inhibitor therapy in metastatic renal cell carcinoma.[53] In addition, cavitation of lung metastases on contrast-enhanced CT observed during treatment with regorafenib was associated with the absence of progression at Week 8 in a retrospective study of 75 mCRC patients.[54] Similarly, a prospective study examined tumour attenuation (in Hounsfield units) in contrast-enhanced CT and the cavitary changes of lung metastases in 80 regorafenib-treated mCRC patients.[55] While this study was largely inconclusive (no differences in DCR, PFS, or OS were observed based on radiological changes),[55] the role of CT density changes as biomarkers for regorafenib is undergoing further investigation.

Other potential biomarkers are emerging in the literature; for example, a study showed that resistance of mCRC to regorafenib is associated with mutations of the FBW7 tumour suppressor and that FBW7 mutational status is a key genetic determinant of mCRC response to targeted therapies such as regorafenib.[56] PUMA expression may be useful as an indicator of regorafenib sensitivity in mCRC,[7] whereas p-STAT3 expression was identified as a potential biomarker in HCC.[6] To identify new biomarkers, the RELAIS multicentre translational biomarker Phase II trial (EudraCT: 2014-004927-27) of regorafenib in non-resectable pretreated mCRC patients is currently investigating circulating tumour DNA as an indicator of regorafenib efficacy in terms of OS.[57] There is also an ongoing Phase II study (NCT01949194) that aims to identify biomarkers in mCRC patients treated with single-agent regorafenib who have failed one prior treatment.[58]

PREVENTION AND MANAGEMENT OF REGORAFENIB-RELATED TOXICITIES

Despite the reported benefits of regorafenib in various cancers, treatment-related AEs may limit its clinical use. As these AEs typically occur early, close monitoring of patients immediately following commencement of regorafenib therapy is strongly recommended. Some AEs may be managed by incorporating simple prophylactic measures, as outlined by Sastre et al.[59] For example mild soaps, intense hydration, and comfortable clothes, as well as non-urea-based skin creams should be recommended to patients to prevent skin toxicities, and keratolytic creams should be recommended for hyperkeratotic lesions. Other regorafenib-related AEs may be managed in the clinical setting with dose modifications. Indeed, dose modifications were frequently required to manage regorafenib-related toxicities in GIST patients in long-term follow-up (median follow-up of 41 months) from the multicentre Phase II GRID trial.[48] Therefore, the Phase II randomised ReDOS Study (NCT02368886) is currently exploring novel strategies to improve the tolerability of regorafenib.[60] These include the use of a steroid (clobetasol propionate) cream to alleviate HFSR, as well as using incremental regorafenib dose escalations (starting at 80 mg/day, with weekly dose escalations until the goal of 160 mg is reached).[60]

CONCLUSIONS AND FUTURE DIRECTIONS

The collective clinical trial data indicate that regorafenib has good efficacy in patients with different types of advanced or refractory GI

cancers who have progressed on prior standard therapy. In addition to the FDA-approved use of regorafenib in advanced mCRC and GIST following progression on standard therapies, data from the RESORCE study suggest that regorafenib can also be used as a second-line therapy in advanced HCC patients who have progressed on sorafenib. Further clinical evaluation of the use of regorafenib as either a first, second, or third-line therapy, alone, or in combination with chemotherapy, in gastric/oesophageal cancer, pancreatic cancer, soft tissue carcinomas, and metastatic bone sarcomas, is required. Investigating the utility of this drug in cancers beyond the GI tract is also warranted.

Future studies relating to regorafenib in GI cancers should aim to decipher whether ethnicity, pretreatment approaches, or other prognostic factors can affect patient outcomes. The identification of biomarkers would also help us to accurately select the appropriate population(s) to treat with regorafenib in clinical practice. Currently, the main downside of regorafenib therapy is its toxicity profile; a high incidence of HFSRs and fatigue has been observed in the real-world setting. While these toxicities can generally be managed in the clinic with appropriate dose modifications, novel strategies such as steroid creams should be explored to improve the tolerability of regorafenib.

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COILS FOR THE TREATMENT OF ADVANCED EMPHYSEMA: A GROWING BODY OF EVIDENCE AND ROUTINE EXPERIENCE

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ABSTRACT

Endoscopic lung volume reduction (ELVR) mainly comprises endobronchial valves (EBV) and endobronchial coil (EBC) implants. EBV aims to occlude the most diseased and/or hyperinflated lobe thus inducing complete atelectasis. EBC therapy was developed a few years ago and is applicable independently of collateral flow and in patients presenting with disease dispersed throughout the upper and lower lobes. Bronchoscopic lung volume reduction with EBC is feasible in a wider range of patients (irrespective of collateral flow or disease homo/heterogeneity) than for EBV, and provides clinical benefits in the short-term, associated to an acceptable safety profile. The growing clinical and commercial experience of ELVR with nitinol coils will be reviewed in this article.

Keywords: Coil, emphysema, surgical management, endoscopic lung volume reduction (ELVR).

INTRODUCTION

Emphysema is a progressive subtype of chronic obstructive pulmonary disease (COPD) which can be particularly debilitating in its advanced stages.[1] The aetiology of emphysema is mainly environmental (smoking and pollution) and leads to the destruction of alveolar walls, irreversible airway obstruction, loss of elastic recoil, air trapping, and thus a reduced gas exchange area. This subsequently generates lung hyperinflation, flattening of the diaphragm, dyspnoea, and poor clinical outcomes with potentially life-threatening complications.[2-5] COPD is incurable and the core of its medical management is aimed at reducing symptoms and disease progression, with smoking cessation, short and long-acting bronchodilators, pulmonary rehabilitation, and oxygen supplementation. In severe emphysema, beyond medical therapy, lung volume reduction, which can be achieved by surgical or endoscopic techniques, redirects airflow to less affected regions.

Lung transplantation and lung volume reduction surgery (LVRS) are the two main surgical modalities demonstrated to improve clinical and functional outcomes.[6] LVRS is the surgical removal of diseased portions (20–35%) of the lung parenchymal volume and aims to improve the efficiency of the remaining intercostal muscles, diaphragm, and lung structure. The National Emphysema Treatment Trial (NETT)[6] demonstrated that LVRS is mainly beneficial in patients with heterogeneous, upper-lobe predominant emphysema, low exercise capacity, and low baseline perfusion to the upper lobes.[6-11] Nevertheless, advanced emphysema is frequently diagnosed in cases with older, frail patients, in which lengthy hospitalisations, long recovery periods, and possible surgical morbidity need to be taken into account.[12-15] For this patient subpopulation, available therapeutic options for severe emphysema are still limited; less invasive techniques to address this unmet need have been developed over the past decade.

This review aims to report on the clinical data available to date (including trial and real-life evidence) on the use of coil therapy for advanced emphysema.

Table 1: Overview of the clinical data available to date on coil therapy in emphysema.

Type of study	n	Indication	Procedure	Coil therapy	Final follow-up	FEV_1 (change, %), MCID ≥12%[41]	FEV_1 % responder rates	FVC (change)	RV (change), MCID ≥0.35[47]		6MWT (change), MCID ≥26 m[48]		SGRQ (change, points), MCID ≥4 points[49]		Study
Pilot Studies															
Single-centre prospective cohort pilot study	11	Heterogeneous and homogeneous emphysema			3M	-5.0±2.9		-1.5±6%	+3.3±4.6%		+5.6±8.5%		-6.1±4.4	79%	Herth et al. 2010[22]
Single-centre prospective cohort pilot study	16	Heterogeneous emphysema	12 bilateral, 4 unilateral treatment	Median 10 coils /patient	6M	+14.9±17.0	64%	+13.4±12.9%	-11.4±9.0%	64%	+84.4±73.4 m	86%	-14.9±12.1		Slebos et al. 2012[35]
Prospective Studies															
Multicentre European feasibility study	60	Heterogeneous and homogeneous emphysema	55 bilateral, 5 unilateral treatment (34 patients completed 12 months follow-up)	Median 10 coils /patient	6/12M	6M: +10.0±21.0% 12M: +8.9±22.2%	48%	6M: +0.20±0.53 L 12M: +0.28±0.45 L	12M: -0.71±0.81 L	65%	+51.4±76.1 m	53%	-11.1±13.3	74%	Deslee et al. 2014[32]
Single-centre prospective cohort pilot study	10	Homogeneous emphysema and hyperinflation		Median 11 coils /lobe	6M			+0.39 L	-0.6 L	70%	+61 m	70%	-15	70%	Klooster et al. 2014[33]
Retrospective Study															
Single-centre retrospective analysis	26	Heterogeneous emphysema and incomplete fissures			6M	0.04±0.12 L	43%		-0.42 L		32±60 m	69%	-6		Kontogianni et al. 2014[36]
Randomised Clinical Trials															
RESET Trial															
Multicentre randomised clinical trial	23	Heterogeneous and homogeneous emphysema			3M	13.8±18.1%	57%	9.5±14.1%	-7.1±10.5%	57%	56.0±65.1 m	74%	-4.7±13.4	65%	Shah et al. 2013[37]
	24		(22 controls treated at crossover)		6/12M	6M: 10.0±21.0% 12M: 8.9±22.2%		6M: 9.6±18.4% 12M: 8.4±16.3%	6M: -5.8±13.6% 12M: -5.4±13.7%		6M: 54.6±54.2 m 12M: 34.1±52.4 m		6M: -7.3±12.2 12M: -6.1±14.0		Zoumot et al. 2015[38]
RENEW Trial															
Multicentre randomised clinical trial	315	Heterogeneous and homogeneous emphysema	Usual care plus bilateral coil treatment Usual care alone	158 157	12M		+7.0% (p<0.001)				+14.6 (p=0.02)		-8.9 points (p<0.001)		[31,34,39]

Table 1 continued.

Type of study	n	Indication	Procedure	Coil therapy	Final follow-up	FEV_1 (change, %), MCID ≥12%[41]	FEV_1 % responder rates	FVC (change)	RV (change), MCID ≥0.35[47]	6MWT (change), MCID ≥26 m[48]	SGRQ (change, points), MCID ≥4 points[49]		Study
Randomised Clinical Trials													
REVOLENS Trial													
Multicentre randomised clinical trial	100	Heterogeneous and homogeneous emphysema usual care plus bilateral coil treatment usual care alone	Usual care plus bilateral coil treatment (n=50) versus usual care alone (n=50)		6M		+0.09 L (95% CI: 0.05 L to ∞; p=0.001)			+21 m (95% CI: -4 m to ∞; p=0.06)		18%; 1-sided (95% CI: 4% to ∞; p=0.03)	6,11,36,37,40-42
					12M		+0.08 L (95% CI: 0.03 L to ∞; p=0.002)			21 m (95% CI: -5 m to ∞; p=0.12)		-10.6 points (95% CI: -5.8 points to ∞; 1-sided p<0.001)	

3M: 3 months; 6M: 6 months; 12M: 12 months; 6MWT: 6-minute walk test; FEV_1: forced expiratory volume in the first second; FVC: forced vital capacity; MCID: minimal clinically important differences; RV: residual volume; SGRQ: St George's Respiratory Questionnaire.

ENDOSCOPIC LUNG VOLUME REDUCTION

Endoscopic lung volume reduction (ELVR) mainly comprises endobronchial valves (EBV) and endobronchial coil (EBC) implants. EBV aims to occlude the most diseased and/or hyperinflated lobe, thus inducing complete atelectasis.[16-18] However, the patient subset most likely to benefit from EBV is narrow and only allows patients with absence of interlobar collateral flow (i.e. collateral ventilation).[19-21] Nitinol coil therapy was developed a few years ago and is applicable in a wider range of patients, independently of collateral flow.[22] Other ELVR techniques involve the use of a sealant to collapse diseased tissue,[23-25] thermal airway ablation,[26,27] and airway bypass, but these therapeutic modalities have only achieved limited success and are not currently in commercial use.[28] Consequently, the growing clinical and commercial experience of bronchoscopic lung volume reduction with nitinol coils will be reviewed in this article.

ENDOBRONCHIAL COIL THERAPY IN ADVANCED EMPHYSEMA

Principle and Device Technology

EBC implants are nitinol (nickel-titanium) shape-memory devices designed to restore lung elastic recoil through the compression of diseased lung parenchyma and the shortening of the airway, thereby increasing regional radial tension. Their mechanism of action is thus unique, as it does not rely on atelectasis. Tissue re-tensioning improves lung mechanics, prevents airway collapse, and hyperinflation. These translate into clinical benefit, with significant improvements in exercise capacity, and, to some extent, improvements in forced expiratory volume in the first second (FEV_1).[29] Coil treatment success is not dependent on specific placement within the patient's anatomy and coils do not migrate/dislodge (three sizes are currently available; total length: 100/125/150 mm).[30]

Bronchoscopic Procedure

Computed tomography (CT)-based patient selection is first conducted to exclude patients with severe bullous disease, suspicious nodules, active infection, bronchiectasis, small airway disease, severe paraseptal emphysema, or insufficient residual parenchyma.[31] The objective of treatment is to distribute approximately 10 coils sub-segmentally, evenly throughout the lobe under

fluoroscopic guidance. About 10 coils per lobe are set in place and deployed via a specific catheter into their three-dimensional form, but larger lower lobes may require more coils.[32,33] The procedure time is 30–40 minutes, depending on patient anatomy and physician experience.[34] Coil treatment is a sequential bilateral treatment; when treating two contralateral lobes, two separate procedures are involved.

AVAILABLE EVIDENCE BASE FOR COIL THERAPY FOR THE TREATMENT OF ADVANCED EMPHYSEMA

Available Clinical Data to Date

Eight clinical publications describing coil treatment of severe emphysema are currently available, including three published, randomised, controlled trials. Main details on study design, and both clinical and safety outcomes are reported in Table 1.

RECENTLY COMPLETED TRIALS

RENEW Trial

The RENEW trial (NCT01608490) was a pivotal US Food and Drug Administration (FDA)-approved, multicentre, 1:1 randomised clinical trial conducted in 26 centres, including 5 in Europe and 1 in Canada, totalling 315 enrolled patients.[31,34] The study aimed to evaluate safety and effectiveness of coil treatment versus standard medical care with a primary endpoint of 12-months, 6-minute walk test (6MWT), and secondary outcomes of quality of life (QoL) (St George's Respiratory Questionnaire [SGRQ]) and lung function (FEV_1). Patients with heterogeneous and homogeneous emphysema were included; control patients could receive treatment via a separate FDA-approved protocol at the 1-year study exit.

In December, BTG plc (BTG International Ltd., London, UK) announced that all primary and secondary endpoints of the study had been met, with results published in May 2016.[34,39] A statistically significant 14.6 m benefit in change in the 12-months 6MWT was observed over the control group (p=0.02). Similarly, other statistically significant and clinically meaningful improvements versus control group patients in QoL (SGRQ, mean improvement of 8.9 points, p<0.001) and lung function were reported (FEV_1, mean improvement: 7.0%, p<0.001). The respective safety profiles of treatment and control groups were as expected in such patient populations (mostly GOLD IV) and included pneumonia, pneumothorax, lower respiratory tract infections, respiratory failure, haemoptysis, COPD exacerbation, and dyspnoea occurring at a higher rate in the active treatment arm.

REVOLENS Trial

In 2012, the French Ministry of Health approved and funded the multicentre, randomised REVOLENS clinical trial (NCT01822795). REVOLENS was conducted in 10 French university hospitals in order to evaluate 6 and 12-month efficacy, safety, and cost-effectiveness of endobronchial nitinol coil therapy.[40] This superiority trial encompassed 100 patients (71% male; mean age: 62 years), 1:1 randomised to either usual care, i.e. rehabilitation and bronchodilators with or without inhaled corticosteroid and oxygen therapy, or usual care plus bilateral coil treatment with the placement of nitinol coils in both pulmonary lobes.

The primary outcome was exercise capacity improvement of ≥54 m in the 6MWT at 6 months (one-sided hypothesis test). Secondary outcomes included changes at 6 and 12 months in the 6MWT, lung function, QoL as assessed by SGRQ (range: 0–100, minimal clinically important difference ≥4), morbidity, mortality, total cost, and cost-effectiveness. Lung function evaluation comprised FEV_1, forced vital capacity (FVC), residual volume (RV), total lung capacity (TLC), and RV/TLC ratio. Safety was evaluated as adverse event (AE), serious adverse event (SAE) occurrences, and SAE composite scores over the 12-month follow-up period. Patients were followed-up for 12 months.

Efficacy outcomes

Most of the patients assigned to the coil therapy group (94%, n=47) completed bilateral treatment and received a mean of 9.8 coils per procedure. After 12 months, 44 and 47 patients from the coil and the usual care groups were available for follow-up, respectively.

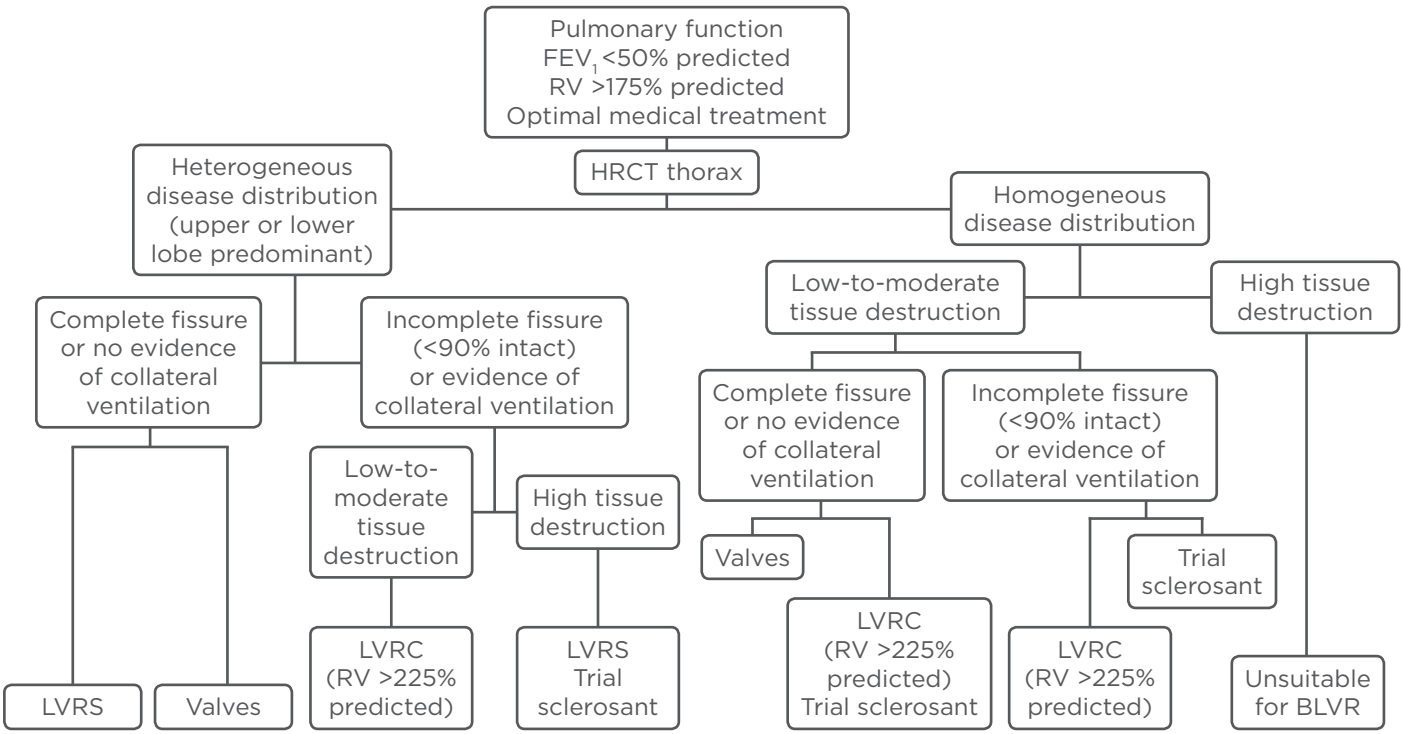
Post-procedure results at 6 months

At 6 months, coil therapy was significantly superior to usual care as the primary endpoint was achieved, with 36% and 18% of patients (evaluable data, n=44 for both groups) reaching an improvement of ≥54 m in the 6MWT from the coil and usual therapy treatment arms, respectively (between-group difference [BGD] of 18%; 1-sided 95% confidence interval [CI]: 4% to ∞; p=0.03).

Table 2: Demographic and bronchoscopic procedure characteristics of the patients at baseline.

Variable	
Age (years)	68±7.7
BMI (kg/m^2)	22±6.1
FEV_1 (L)	0.78±0.29
FEV_1 (% predicted)	31±10
DLCO (% predicted)	38±14.6
RV (% predicted)	227±60
6MWD (m)	310±112
SGRQ	61.8±12.8
Treatment 1: total bronchoscopy time (min)	32.5±10.9
Treatment 1: fluoroscopy time (min)	9±4.2
Treatment 1: number of coils	12±1.38
Treatment 2: total bronchoscopy time (min)	30±11
Treatment 2: fluoroscopy time (min)	8±2.66
Treatment 2: number of coils	11±1.95

Values are reported as median±SD.
6MWD: 6-min walk distance; DLCO: diffusing capacity of the lung for carbon monoxide; FEV_1: forced expiratory volume in the first second; RV: residual volume; SGRQ: St. George's Respiratory Questionnaire; SD: standard deviation.



For any emphysema, a lung transplant should be considered.

Figure 1: Treatment algorithm for bronchoscopic lung volume reduction in patients with severe emphysema.
BLVR: bronchoscopic lung volume reduction; FEV_1: forced expiratory volume in 1 second; HRCT: high-resolution computed tomography; LVRC: lung volume reduction coil; RV: residual volume; LVRS: lung volume reduction surgery.

Significantly different findings were also observed in the secondary endpoints, with 6MWT improvements favouring coil therapy over usual care, the BGD being statistically significant as percentage changes from baseline: 6 months, BGD of +8% (95% CI: -2.7 m to ∞; p=0.048); 12 months, BGD of 7.1% (95% CI: -2.2 m to ∞; p=0.09). At 6 months, coil therapy was significantly superior to usual care in terms of FEV_1 (BGD of +0.09 L [95% CI: 0.05 L to ∞; p=0.001]) and for the other secondary efficacy endpoints (FVC, RV, RV/TLC ratio, Modified Medical Research Council [MMRC] dyspnoea scale, Transition Dyspnea Index [TDI], and SGRQ; all p<0.05). QoL improvement (SGRQ) was superior in the coil treatment group over usual care with a BGD of -13.4 points (95% CI: -8 points to ∞; one-sided; p<0.001).

Post-procedure results at 12 months

At 12 months, BGD were significant (p<0.05) in all endpoints but the 6MWT. As an example, BGD for FEV_1 was +0.08 L [95% CI: 0.03 L to ∞; p=0.002]), again demonstrating statistically significant superiority of coils over usual care. However, the observed BGD did not reach the minimal clinically important difference of 0.1 L.[41] QoL improvement (SGRQ) was sustained at 12 months with superior outcomes in the coil treatment group over usual care (BGD of -10.6 points; 95% CI: -5.8 points to ∞; one-sided; p<0.001). Of note, there was no difference in efficacy between heterogeneous and homogeneous emphysema at both time points.

Safety outcomes

During the 12-month follow-up period, four deaths (8%) were reported in the coil group versus three deaths (6%) in the usual care treatment arm (BGD of 2%; 95% CI: -8–12%; p=0.99). The most frequently reported AE was self-resolving haemoptysis (<5 mL) within 30 days post-procedure (48%). SAE composite scores comprised 17 events in 14 patients (28%) in the coil group and 8 events in 6 patients (12%) in the usual care group (BGD of 16%; 95% CI: 1–31%; p=0.046). Pneumonia was the most frequent SAE and was reported for 11 events in 9 patients (18%) in the coil therapy group and 2 events in 2 patients (4%) in the usual care group during the 12-month follow-up period, with a BGD of 14% (95% CI: 2–26%; p=0.03). Overall, these results show that the safety profile of coil therapy as evidenced in this study was consistent with previous clinical findings,[42] and was similar to that of endobronchial valves[43,44] but much improved over LVRS.[6,11]

Health economics

The mean total 1-year per-patient BGD cost was $47,908 (95% CI: $47,879–48,073, p<0.001). The incremental cost-effectiveness ratio was $782,598 per additional quality-adjusted life-year (95% CI: $663,496–1,327,212 per quality-adjusted life-year). However, as the follow-up period was relatively short (12 months), these findings are insufficient to draw conclusions on the long-term cost effectiveness of nitinol coil therapy since the reported short-term costs should be quantified against the long-term benefits gained post-procedure. As such, this study is still ongoing and encompasses a crossover and an extended (5-year) follow-up, including a long-term health economic analysis of all treated patients.

FROM REAL CLINICAL TRIAL EVIDENCE TO REAL-LIFE CLINICAL PRACTICE: DO THE BENEFITS TRANSLATE INTO THE REAL WORLD?

Real-Life Data on the Commercial Experience of Coil Treatment

PneumRx EBC implant received Conformité Européenne (CE-) Mark in 2010. At the American Thoracic Society (ATS) 2014, data extracted from three centres in Northern Germany reported on 49 patients (62 coil procedures) treated with coils.[45] Mean 1-month follow-up data were available for 41 patients (82%); coil treatment led to a considerable improvement of 6MWD after bilateral procedures (+119±135 m; p=0.006; n=20), after the first procedure (44±131 m; p<0.001; n=41), and the second procedure (+64±110 m; p=0.097; n=20). In the bilateral group, such benefits were highly significant and were sustained for at least 1 year post-treatment.

In a retrospective analysis on 26 patients with heterogeneous emphysema and incomplete fissures at Heidelberg University, Heidelberg, Germany,[36] patients were only treated in one lung. Pulmonary function (as assessed by FEV_1 and 6MWT) was improved at 3 months but tended to decrease at 6-month follow-up. QoL (SGRQ) was significantly improved at 3 months. A post-market, observational, prospective, multicentre, European registry is currently recruiting patients.[46]

Experience at Pourtales Hospital, Neuchâtel, Switzerland

Data extracted from the post-market European registry for Neuchâtel Hospital reported on 25 patients with emphysema (48 procedures) treated with coils. Demographic and bronchoscopic procedure characteristics are shown in Table 2. The selection of patients was made according to the algorithm described below. Follow-up data were largely incomplete, being available only for nine patients at 6 months: coil treatment led to a considerable improvement of QoL (SGRQ) after the two procedures (-23.6±9.2, p=0.0009). Pulmonary function (as assessed by FEV_1 and RV) was also significantly improved at 6 months. On the contrary, 6MWD and diffusing capacity of the lung for carbon monoxide did not show any statistically significant change. These very preliminary results are consistent with the already published data.

Treatment Algorithm: Real-Life Clinical Experience

A treatment algorithm for BLVR in patients with severe emphysema is proposed in Figure 1. From our real-life experience and clinical data available to date, BLVR is an option in stable GOLD III/IV patients with homogeneous or heterogeneous emphysema with no massive lung parenchyma destruction and RV ≥175% predicted. Conversely, patients who are not candidates to coil therapy comprise those with severe bullous disease, known pulmonary hypertension, prior surgical lung treatment, chronic steroid use, carbon monoxide diffusing capacity <20% predicted, symptomatic bronchiectasis, and those concurrently receiving any therapeutic anticoagulation or any anti-aggregate therapy other than aspirin.

CONCLUSIONS

Bronchoscopic lung volume reduction with nitinol coils is feasible in a wider range of patients (irrespective of collateral flow) than EBV and provides clinical benefits on the short-term, associated to an acceptable safety profile. However, additional clinical data are still needed to establish the long-term benefit-to-risk ratio of coil therapy; it is likely that further results from follow-ups beyond 12 months from randomised clinical trials will provide answers. These clinical trial data, alongside registry/real-life outcome data, will undoubtedly help refine patient stratification and treatment selection and further ascertain BLVR within the expanding therapeutic armamentarium for advanced emphysema.

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EMJ EUROPEAN MEDICAL JOURNAL

New Data About the SERVE-HF Trial and New Horizons for Adaptive Servo-Ventilation Therapy in Central Sleep Apnoea

The following videos discuss the efficacy and safety of adaptive servo-ventilation (ASV) in conditions such as central sleep apnoea.

We bring you a recording of a discussion by a panel of experts entitled **'New Horizons in ASV: Advancing science | informing ASV clinical practice'**. ASV is the standard therapy for central sleep apnoea, and the SERVE-HF trial results have surprisingly shown an increased mortality risk in systolic heart failure (HF) patients with reduced ejection fraction. The panel discusses the implications of the new analysis from the SERVE-HF trial and how ASV should be used in clinical practice.

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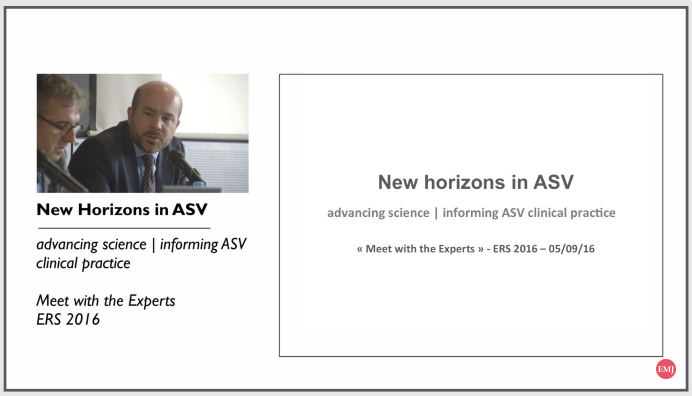

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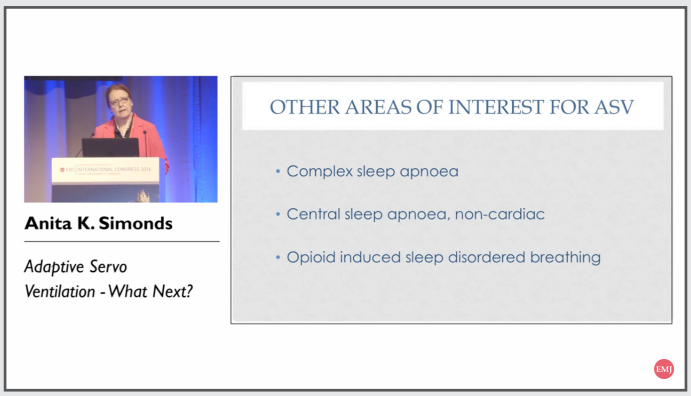

Adaptive Servo Ventilation - What's next?
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NON-TRANSFUSION-DEPENDENT THALASSAEMIA: A PANORAMIC SURVEY FROM PATHOPHYSIOLOGY TO TREATMENT

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ABSTRACT

Non-transfusion-dependent thalassaemia (NTDT) is a rather broad term that encompasses a group of thalassaemia syndromes, most commonly β-thalassaemia intermedia, haemoglobin E/β-thalassemia, and α-thalassaemia intermedia (haemoglobin H disease). Importantly, these entities do not require regular blood transfusions for survival, and therefore have transfusion independence. Clinical morbidities associated with the NTDTs are the end result of the culmination of three principal pathophysiological aberrancies: ineffective erythropoiesis, chronic anaemia (and associated haemolysis), and iron overload. Such complications involve multiple organs and organ systems; hence, the importance of prompt identification of at-risk individuals and holistic management of diagnosed subjects can never be overstated. Several management options, both medical and surgical, remain at the disposal of involved clinicians, with a significant body of data favouring the virtue of iron chelation therapy, fetal haemoglobin induction, and treatment with blood transfusions, the latter only when absolutely indicated, with reservation of splenectomy to a few select cases. Yet, a better understanding of the molecular phenomena at the origin of the disease process in the NTDT syndromes calls for a pressing need to explore novel therapeutic modalities, in light of the increasing incidence of NTDT in the developed world.

Keywords: Non-transfusion-dependent thalassaemia, anaemia, iron overload, complications, chelation.

INTRODUCTION

Inherited haemoglobin disorders are divided into two main groups: 1) thalassaemia α and β with defective globin chain synthesis in adult haemoglobin and 2) structural haemoglobin variants S, C, and E. Thalassaemia can be associated with a myriad of phenotypes as a result of simultaneous inheritance of two different thalassaemia mutations, one from each parent, or possibly its co-inheritance with structural haemoglobin variants. In fact, multiple classification systems have been developed to categorise the thalassaemia syndromes, but transfusion dependence probably remains the most important criterion in classifying thalassaemias and differentiating between their severities. Transfusion-dependent-thalassaemias (TDTs) constitute the more severe end of the disease spectrum and include α-thalassaemia major (TM) and β-TM. On the other hand, non-transfusion-dependent thalassaemias (NTDTs) describe patients who do not require life-long transfusions for survival, allowing that transfusions might still be required in particular clinical scenarios. The term 'NTDT' includes β-thalassaemia intermedia (TI), haemoglobin E/β-thalassaemia, and α-TI (or haemoglobin H disease), in addition to the much rarer forms of haemoglobin S/β and C/β-thalassaemia.

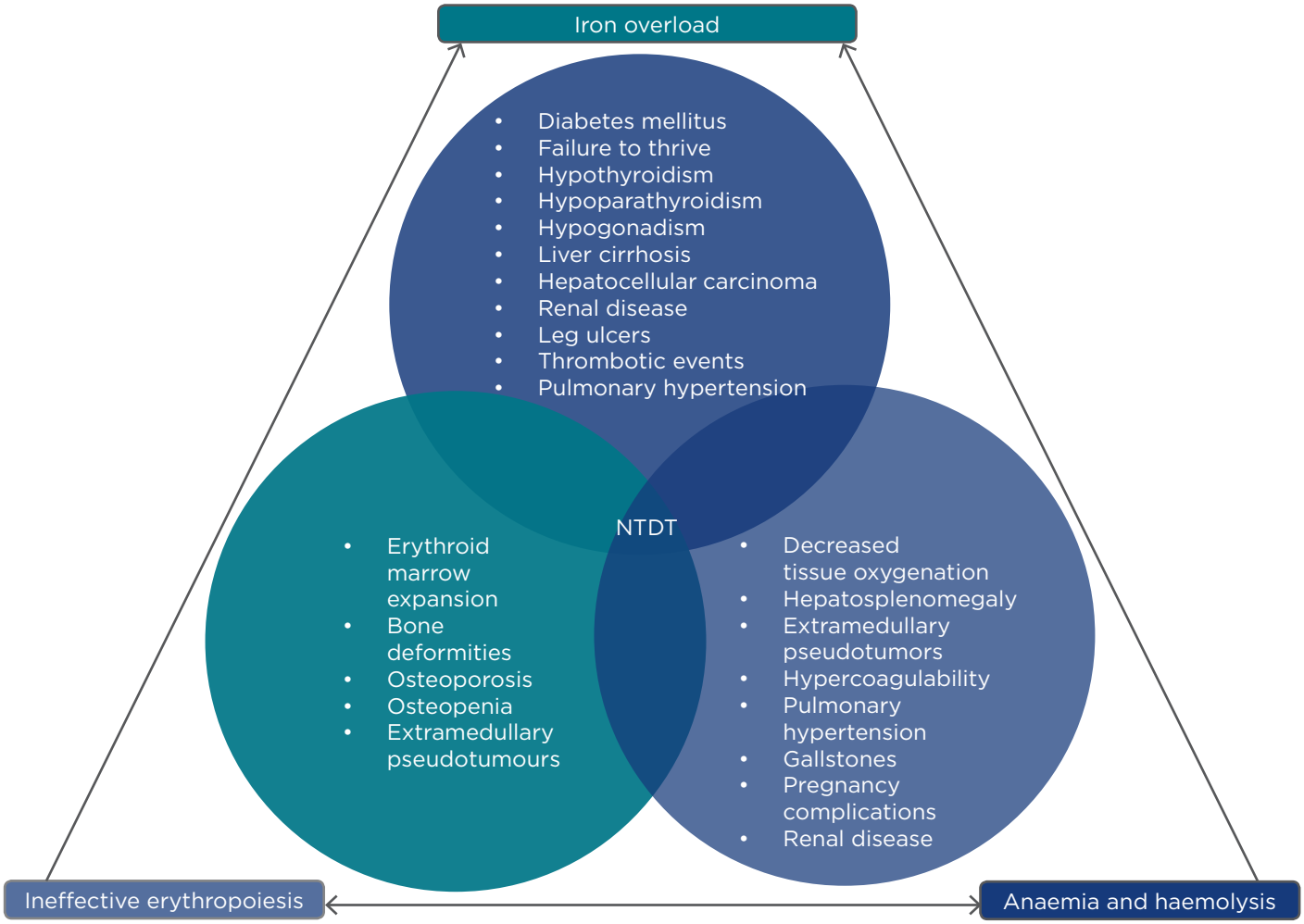

Figure 1: Pathophysiological cornerstones in non-transfusion-dependent thalassaemia and their associated complications.
NTDT: non-transfusion-dependent thalassaemia.

EPIDEMIOLOGY

Thalassaemia constitutes a major public heath burden despite its decreasing prevalence in the last few years. α-thalassaemia remains the most common thalassaemia, with 1 million individuals affected by the various α-thalassaemia syndromes worldwide. Whereas 5% of the world population are carriers of α-thalassaemia, 1.5% (80 million) are carriers of β-thalassaemia, most of whom are transfusion-dependent. The difference between the prevalence of the transfusion-dependent (e.g. TM) and transfusion-independent syndromes is not clear, especially that data on the epidemiology of the latter are limited. In general however, NTDTs are especially relevant in the Sub-Saharan African and Mediterranean regions due to the high prevalence of consanguineous marriages in these parts of the world. Interestingly, a protective role against malaria acquisition has been associated with the genetic polymorphisms underlying the various thalassaemia syndromes, which might partially explain the relatively high frequency of the latterin malaria-infested areas.[1,2]

PATHOPHYSIOLOGY AND COMPLICATIONS

The pathophysiology of NTDT, similar to that of the other thalassaemia syndromes, can be portrayed as haemoglobin chain imbalance and ensuing oxidative damage.[3] The pathophysiological derangements defining NTDT are usually clustered under the all-encompassing triad of ineffective erythropoiesis (and associated compensatory extramedullary haematopoiesis), chronic anaemia and related haemolysis, and iron overload (Figure 1).[1] The complications associated with NTDT are intertwined with the aforementioned triad, while other complications can be regarded

as subcategories of these three processes. In this section, we outline the principal complications of NTDT at the level of various organ systems.

Blood-Related Complications

Iron overload

Hepcidin is an inflammatory protein responsible for removing iron from the circulation and promoting its entrapment in macrophages and liver cells. It also decreases iron absorption from the gut and is therefore one of the main regulators of iron entry into the body.[4] In states of abnormally low hepcidin levels in the blood, such as in NTDT, an excess of iron is absorbed by the gut with increased export from from reticuloendothelial cells.[5] The end result is an inevitable drastic increase in free iron in the circulation, which itself incites oxidative damage and brings about end-organ compromise.[5] It is worth noting that although transfusion therapy is the main mechanism of iron overload in TDT, occasional transfusions due to complications in NTDT contribute, to a lesser extent, to the iron overload state.[1] Similar to TDT, iron overload in NTDT is managed by chelation therapy which is only indicated in NTDT patients if iron concentrations reach threshold levels associated with increased iron-related complications.[6] These threshold values include liver iron concentration ≥5 mg/g of dry weight, or, in the absence of liver iron concentration measurement, serum ferritin level ≥800 ng/mL in patients >10 years old (or 15 years in haemoglobin H disease).[6]

Hypercoagulable state

In general, thromboembolic phenomena related to thalassaemia are 4.38-times more common in TI than in TM.[7] The aetiology of the hypercoagulable state in the thalassaemia syndromes, and NTDT in particular, is multifactorial.[7] Incriminated are the procoagulant activity of haemolysed circulating red blood cells and associated increased platelet activation, coagulation factor defects, depletion of antithrombotic factors, and endothelial inflammation.[8] Splenectomy is an additional risk factor provided that one-third of the total platelets are normally sequestered in the spleen.[9,10] A study by Taher et al.[11] determined that splenectomised TI patients who experience thromboembolic events in association with a hypercoagulable state are characterised by a high nucleated red blood cell count (≥300×10^6/L) and a high platelet count (≥500×10^9/L). They are also more likely to have evidence of pulmonary hypertension and be transfusion-naïve. Nucleated red blood cells, in particular, demonstrate the presence of adhesion molecules which might contribute to the hypercoagulable state seen in patients with thalassaemia.[12]

Pulmonary hypertension

Another pressing haematological complication in thalassaemics is pulmonary hypertension[13] which is a serious condition and requires urgent intervention. Pulmonary hypertension is diagnosed when tricuspid valve regurgitant jet velocity is found to exceed 2.5–2.8 m/s, the equivalent of a pulmonary arterial systolic pressure of 30–35 mmHg.[2,14-19] Although believed to be due to vasculopathy resulting from excessive haemolysis combined with nitric oxide depletion and enhanced platelet activation, the exact mechanism underlying the association between pulmonary hypertension and thalassaemia remains unknown.[20,21] However, it was observed that nucleated red blood cells might be involved in the mechanisms accounting for pulmonary hypertension after splenectomy, possibly due to their effect on the coagulation system.[12,22]

Pulmonary hypertension is 5-times more prevalent in NTDT than in TM as revealed by right heart catheterisation.[23] On the other hand, it was observed that transfusions significantly reduced pulmonary hypertension in patients with thalassaemia.[2,18,24] This, however, needs to be reproduced in clinical trials before a definite conclusion can be drawn.

Iron overload cardiomyopathy

Iron overload cardiomyopathy (IOC) is a form of dilated cardiomyopathy characterised by a decrease in the left ventricular ejection fraction due to left ventricular chamber dilation. Although IOC is usually present in TDT, a NTDT-like pattern of iron overload attributable to abnormally low levels of hepcidin in the circulation is usually also present.[25] However, data is lacking on whether IOC can be associated with NTDT, especially since cardiac iron overload is by far a less important concern in NTDT than it is in TDT.

Other haematological complications

Other haematological abnormalities observed in NTDT include haemolytic crises and silent brain infarcts,[1,2] but these are much less prevalent than the above-mentioned disease entities and therefore will not be discussed further.

Extramedullary Haematopoiesis

As previously mentioned, one of the hallmarks of thalassaemia is ineffective erythropoiesis which entails insufficient bone marrow function. This failure to meet circulatory demands drives the body to reinitiate extramedullary haematopoiesis as a compensatory mechanism, a process normally engaged in fetal organs during gestation. This phenomenon can take place almost anywhere in the body but most commonly involves the spleen and liver[4] which explains the hepatosplenomegaly often noted in thalassaemia patients. Also involved, though to a lesser extent, are the lymph nodes, thymus, heart, breasts, prostate, broad ligaments, kidneys, adrenal glands, pleura, retroperitoneal tissue, skin, peripheral and cranial nerves, and spinal canal.[26-30] Interestingly, a recent case report by Cuttler et al.[31] brought attention to extramedullary haematopoiesis in the conjunctiva of a myelofibrosis patient, which suggests a high index of suspicion should be maintained for extramedullary haematopoiesis in unusual anatomical locations. An especially problematic occurrence remains to be paraspinal extramedullary haematopoiesis which usually presents as pseudotumours[1] that can cause a variety of neurological symptoms due to spinal compression. Yet 80% of cases remain asymptomatic[1] and lesions reported in these patients are incidentally discovered on imaging studies performed for other purposes. It should be noted that extramedullary haematopoiesis is far more commonly observed in NTDT than in TDT because NTDT patients do not receive regular transfusions and usually present with chronic haemolytic anaemia.[1]

Hepatobiliary Complications

α/β globin chain imbalance causes red blood cell instability leading to haemolysis which can in turn contribute to the formation of gallstones.[1] Gallstones increase the risk of cholecystitis, a potentially fatal complication in splenectomised patients.[32]

Another menacing hepatobiliary complication in NTDT is liver damage stemming from iron accumulation in the liver parenchyma.[1] Iron deposition in the liver causes fibrosis and eventually cirrhosis, thereby increasing the risk of hepatocellular carcinoma (HCC).[1] Furthermore, NTDT patients who eventually require blood transfusions are at risk of developing viral hepatitis[2] which further inflates the incidence of HCC development. This has prompted the strong recommendation of vaccination against hepatitis B virus for primary prevention of hepatitis B and hepatitis B virus-related HCC,[2] in addition to regular screening with biannual liver ultrasonography and serum α-fetoprotein levels for timely detection of high-risk lesions and apt intervention directed at tumourigenic foci.[2]

Endocrine and Bone Disease

Endocrine gland dysfunction is a common morbidity in NTDT although its prevalence is generally higher in TM.[33] Clinical, radiological, and biochemical studies have confirmed the correlation between iron overload and endocrine gland toxicity.[1] Unlike skeletal deformities and growth delay, which are more commonly encountered in TM, hypothyroidism, hypoparathyroidism, adrenal insufficiency, diabetes mellitus, and hypogonadism are more prevalent in NTDT.[2,18,34] On the other hand, although more common than in TDT, hypothyroidism, hypogonadism, and diabetes mellitus remain quite rare in NTDT.[35] In addition, patients with TI generally have normal sexual development and are usually fertile despite the fact that they tend to experience puberty late.[35] Importantly, the OPTIMAL CARE study concluded that iron chelation decreases the risk of such complications.[18] Iron overload, in addition to nutritional imbalance and increased erythron (due to ineffective erythropoiesis), also explains the occurrence of osteoporosis, osteopenia, and other low bone mineral density states in NTDT patients.[4,36,37]

Leg Ulcers

NTDT patients are at a higher risk of developing leg ulcers in comparison with regularly transfused TM patients.[1,38] This risk increases with age[38,39] meaning that approximately one-third of poorly treated NTDT patients will eventually develop leg ulcers. The pathophysiology of leg ulcers in NTDT can be explained by tissue fragility and eventual ulceration.[2] The key factor in the pathogenesis of this complication is reduced tissue oxygenation, which is believed to be due to the combination of anaemia, hypercoagulability, and ineffective erythropoiesis.[18,32,37]

Pregnancy-related Complications

Females with NTDT have a high risk of developing pregnancy complications ranging from preterm delivery to intrauterine growth restriction (IUGR)

and spontaneous abortion.[40] A series by Nassar et al.,[41] one of the largest of its kind for pregnant NTDT females, showed that 57.1% of pregnancies in this patient population are complicated by IUGR. It also revealed that blood transfusions during pregnancy, although potentially associated with complications, do decrease the risk of IUGR as well as other complications because anaemia is physiologically exaggerated in all pregnant women.[41] In healthy pregnant females, the haemoglobin level should be kept >10 g/dL for optimal development of the fetus.[42] However, according to a case series by Origa et al.[40] of pregnant women with NTDT, targeting the 10 g/dL cut-off proved to be of clinical benefit to only 78% of the patients and their fetuses, where the fetuses of the other 22% ended up suffering from IUGR. This suggests that, apart from the absolute concentration of haemoglobin in the blood, transfusion therapy should be tailored to the cardiac function and general condition of the mother as well as the growth status of the fetus.[40]

Another important consideration in pregnant NTDT female patients is the possible limitation of uterine enlargement by an enlarged spleen, potentially necessitating splenectomy during gestation or shortly after delivery.[41,43]

Renal Complications

Renal complications in NTDT and the other thalassaemia syndromes are multifactorial in aetiology. Anaemia in and of itself affects the glomerulus by causing hyperperfusion and consequently hyperfiltration.[1,44,45] Moreover, chronic hypoxia causes proximal tubular cell dysfunction which leads to interstitial fibrosis and other forms of progressive renal disease.[46] Kidney function can also be compromised by the oxidative stress resulting from the iron burden. Furthermore, deferasirox, an iron chelator used by NTDT patients, has been noted to cause renal toxicity on rare occasions, which has prompted the recommendation of monthly renal function monitoring in deferasirox users.[6] On a separate note, a recent report by Ricchi et al.[47] on three cases of renal malignancy in TM patients highlights the tumourigenic role of hypoxia-inducible factors and of the iron-induced oxidative damage incurred by the renal parenchyma. In theory, provided that both chronic hypoxia and iron overload are also present in TI, it can be speculated that NTDT might represent a preneoplastic state at renal level, but much investigation into this matter is required before such a conclusion can be inferred.

Malignancies

In general, thalassaemia patients today are more likely to develop malignancies of several organs, especially HCC and haematological cancers, as a consequence of improved survival.[48] Contributors hypothesised to be linked to the increased cancer risk in thalassaemia patients compared with the general population are iron, transfusion-transmitted viruses, transfusion-related immunosuppression, and haematopoietic drive.[48] Importantly, a recent longitudinal cohort study from Taiwan reported a significantly higher risk of developing cancer in any organ in TDT than in NTDT patients, with a hazard ratio of 6.7.[49] However, additional studies on cancer in thalassaemia are warranted, especially those targeting the epidemiology and pathophysiology of this rising phenomenon.

MANAGEMENT

Figure 2 illustrates the medical and surgical options available for treating NTDT patients. The treatment strategies included in the figure are discussed below.

Medical

Although restricted to those with matched donors, an allogeneically matched bone marrow transplant is potentially curative of thalassaemia.[50] The therapies enlisted in this section do not cure the disease per se but rather ameliorate or nullify associated complications.

Iron chelation

In NTDT, iron chelation therapy is indicated in patients >10 years of age (or 15 years in haemoglobin H disease) if their liver iron concentration is ≥5 mg/g of dry weight or serum ferritin level is ≥800 ng/mL in the absence of liver iron concentration measurement, which have been established as thresholds associated with increased incidence of iron-related complications.[6]

Iron chelating drugs include agents that are given parenterally such as deferoxamine, and others that are given orally, such as deferiprone and deferasirox.[51] Deferoxamine is the oldest iron chelator, and it is usually administered daily as an intravenous infusion over a period of 8 hours.[51] The main limitation of this drug, however, remains poor compliance with its use due to its laborious administration method. On the other

hand, deferiprone, which is the first oral iron chelator, has a very short half-life and so is administered 3-times a day.[52] Although effecting significant decreases in serum ferritin and non-transferrin-bound iron levels, deferiprone has been associated with adverse gastrointestinal and rheumatological events that have greatly limited its use in clinical settings.[53] Although reports on the detailed benefits and efficacy-to-safety ratios of deferoxamine and deferiprone in NTDT patients are still limited, the Phase II THALASSA trial by Taher et al.[54] proved the efficacy of deferasirox, which is orally administered and has a relatively long half-life, in reducing iron overload in NTDT patients. Consequently, deferasirox remains the only iron chelating agent to have been evaluated for use in NTDT and to have received US Food and Drug Administration (FDA) and European Medicines Agency (EMA) approval for iron chelation in NTDT patients.[52]

Fetal haemoglobin inducers

One way of correcting the α/β globin chain imbalance in NTDT is by inducing the production of fetal β-globin-like molecule, also known as γ-globin, which improves the globin chain imbalance by scavenging the excess α chains, hence increasing fetal haemoglobin (or $\alpha_2\gamma_2$) levels and improving erythropoiesis.[2,33,55] Hydroxyurea, a well-known antineoplastic drug with both cytotoxic and antimetabolic effects, has long been used to treat anaemia associated with sickle disease. While sufficient long-term safety data has been established for its use in thalassaemia, hydroxyurea still demonstrates variable response rates where approximately 40% of NTDT patients taking the medication were found in previous studies to experience a 1 g/dL rise in serum haemoglobin.[2,55] Nonetheless, there have been reports from the OPTIMAL CARE study suggesting that hydroxyurea treatment improves various NTDT complications such as extramedullary haematopoietic tumours, leg ulcers, and quality of life.[55]

Recent data support the promising role of the immunomodulator compound thalidomide in effecting a positive erythroid response in patients with NTDT, through fetal haemoglobin induction and/or by exerting its immunomodulatory effects.[56] We strongly believe this deserves to be further explored inNTDT patients in light of the phenomenal rise in haemoglobin levels observed in the two thalidomide-treated patients reported by Fozza et al.[56]

Transfusion therapy

Although NTDT patients are by definition transfusion-independent, transfusion therapy is still needed by these patients in certain clinical situations. Examples of such scenarios include: pregnancy (due to exaggerated anaemia), surgery or any setting with anticipated acute blood loss, infections, and failure to thrive during childhood.[1]

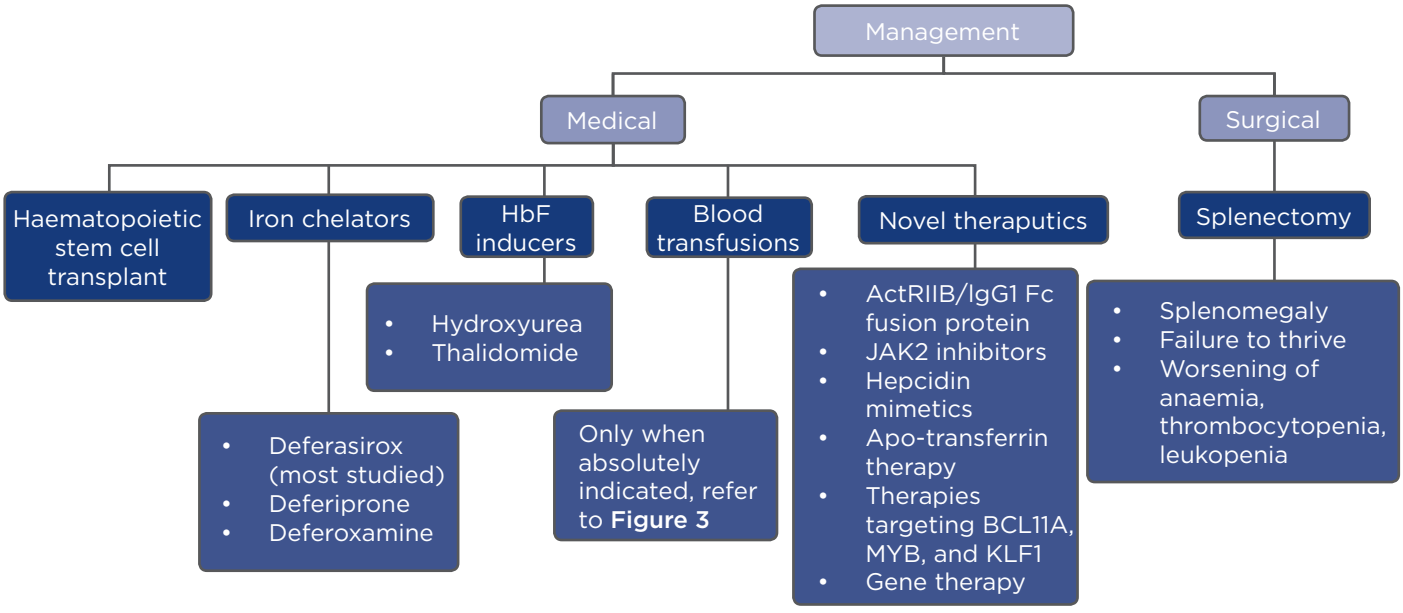

Figure 2: Treatment modalities available for treating non-transfusion-dependent thalassaemia patients.
HbF: fetal haemoglobin.

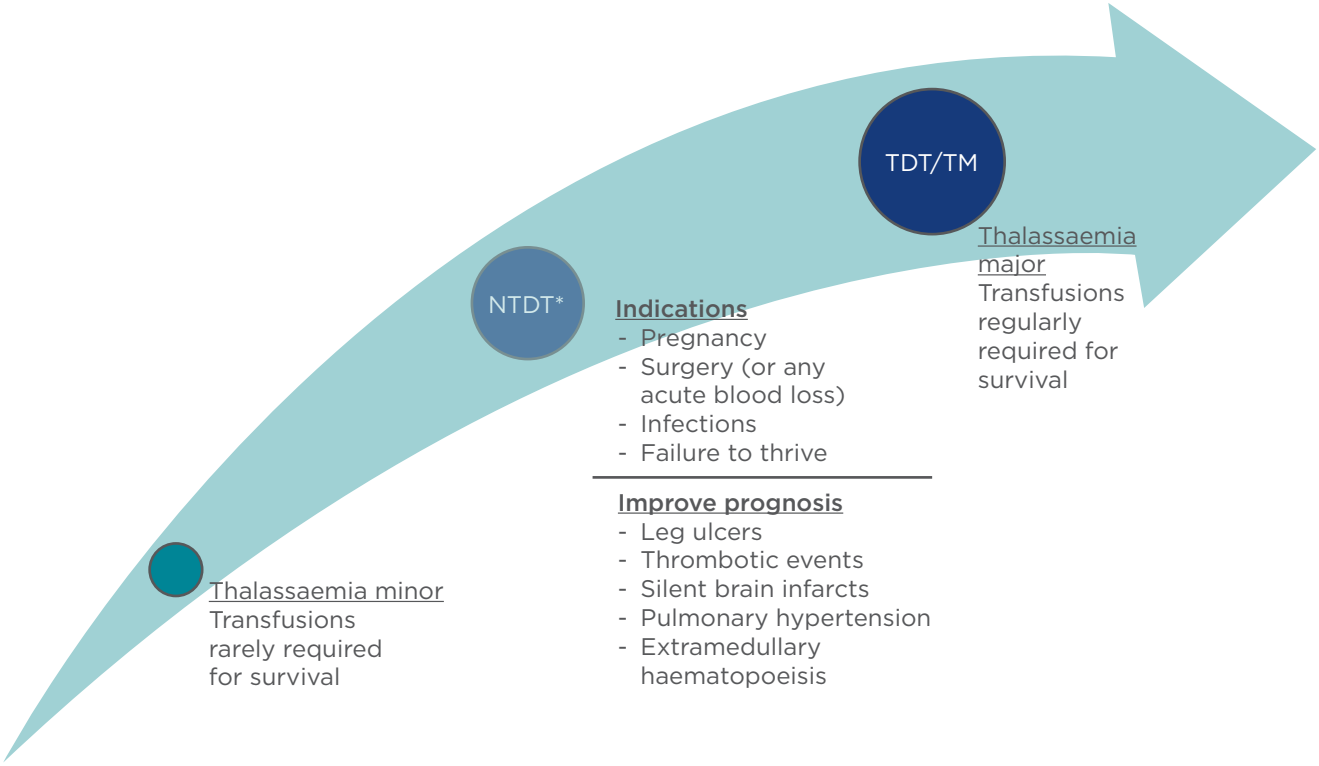

Figure 3: Transfusion requirements across the different thalassaemia syndromes.
*Includes TI.
NTDT: non-transfusion-dependent thalassaemia; TDT: transfusion-dependent thalassaemia; TM: thalassaemia major; TI: thalassaemia intermedia.

In fact, transfusions have been observed to greatly improve the prognosis of certain complications of NTDT such as leg ulcers, thrombotic events, silent brain infarcts, and pulmonary hypertension.[2,20,24,57,58] Blood transfusions can also suppress extramedullary haematopoeisis and its sequelae, particularly paraspinal pseudotumours.[59] Yet, because iron overload is a major concern in NTDT, blood transfusions should not be given to patients in this disease group unless absolutely indicated (Figure 3).

Surgical

The spleen is responsible for the sequestration of one-third of the platelets that are produced by the bone marrow and the removal of pathological red blood cells. In NTDT patients, splenectomy might increase haemoglobin levels by 1–2 g/dL and as such decrease the need for blood transfusions.[33,38] However, splenectomy is associated with a state of hypercoagulability and with increased infection risk (since the spleen contributes to clearing encapsulated bacteria from the body by producing opsonins). In fact, it has been shown that splenectomy is associated with an increased incidence of venous thromboembolic events, silent cerebral infarcts, pulmonary hypertension, and leg ulcers.[60] On that account, splenectomy in NTDT patients is reserved for the following cases:[2,17]

- Worsening of anaemia, thrombocytopenia causing haemorrhages, and/or leukopenia causing recurrent bacterial infections, all as a result of hypersplenism
- Splenomegaly causing early satiety due to gastric displacement, or a palpable, left upper quadrant abdominal mass that might be painful and can eventually rupture
- Poor growth and failure to thrive in cases where transfusions and iron chelating drugs are not possible or unavailable

QUALITY OF LIFE

When managing a thalassaemic patient, applying a patient-centred approach is key to successful outcomes. Equally important to controlling symptoms and preventing complications is assessing the patient's health-related quality of life. It is therefore recommended to closely follow

all patients, both medically and psychologically, while attempting to involve them as much as possible in treatment decision making and providing them with support whenever needed.[2]

CONCLUSIONS AND FUTURE PROSPECTS

The prevalence of NTDTs has recently started to take on a global distribution[33] and thus calls for serious action. Early diagnosis, including prenatal diagnosis and screening, neonatal screening, and treatment of complications in an approach tailored to the individual patient typify the mainstay of managing NTDT patients. Needless to say, preventive measures are central to the management protocol, where the importance of public awareness and premarital counselling and screening cannot be overstated.[61] Also pivotal is the role of reproductive technologies in preventing births of affected children, in addition to the role of education programmes in decreasing marriages between carriers.[61] The strategy combining the aforementioned modalities is often described as the most effective in rapidly reducing the counts of affected births, where its use in Cyprus has led to the eradication of thalassaemia, and its implementation in Lebanon at the Chronic Care Center (the only specialised centre in Lebanon for thalassaemia treatment and prevention) has contributed to a decrease in thalassaemia births in the country of >75%.[61] On a separate note, several novel therapeutics have recently stemmed from a better understanding of the pathophysiological mechanisms underlying NTDT, and many of these strategies are currently being developed in clinical trial programmes. Examples of agents that are currently under investigation are: a recombinant fusion protein comprised of modified activin receptor type IIB (ActRIIB; a member of the transforming growth factor beta superfamily) and human immunoglobulin G1 Fc, Janus kinase 2 (JAK2) inhibitors, hepcidin mimetics, and apotransferrin therapy.[6,33] Other molecules, including *BCL11A, MYB,* and *KLF1* which have been newly identified by human genetic studies, might provide promising therapeutic targets by inducing fetal haemoglobin.[33] Gene therapy is another promising treatment modality that stems from the concept of 'fixing' one's bone marrow cells by transferring the normal α or γ gene into haematopoietic stem cells to permanently produce normal red blood cells.[50] Interestingly, growing evidence over the years has recognised the discerning aptitude of a holistic approach ranging all the way from identification of at-risk populations and implementation of screening and prenatal diagnosis programmes, to comprehensive patient education and patient management strategies targeted at the impairments that adversely impact quality of life, such as anaemia and iron burden.[62-64]

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CLINICAL MANAGEMENT OF DRUG-INDUCED DYSKINESIA IN PARKINSON'S DISEASE: WHY CURRENT APPROACHES MAY NEED TO BE CHANGED TO OPTIMISE QUALITY OF LIFE

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ABSTRACT

Parkinson's disease is a complex, progressive neurodegenerative disorder associated with both motor and non-motor symptoms. Current treatment strategies mainly target the alleviation of motor symptoms through dopaminergic replacement therapy. Many patients with Parkinson's disease will eventually experience motor complications associated with their anti-parkinsonian medication. One of those complications is drug-induced dyskinesia. This paper firstly reviews current approaches to the management of drug-induced dyskinesia, from modifications to the titration of medication, to more invasive approaches like deep brain stimulation. Following this we describe a recent proposal suggesting that the treatment of dyskinesia should be based on the impact on daily activities of patients rather than on the mere presence of the condition. Next, we discuss how this approach could improve the quality of life of patients and their caregivers and finally, we suggest possible ways of implementing this approach in practice.

Keywords: Levodopa-induced dyskinesia, quality of life, caregiver, monitoring.

INTRODUCTION

Parkinson's disease (PD) is a complex, progressive, neurodegenerative disorder associated with multiple neuropathological dysfunctions. One of its features is the degeneration of dopaminergic neurons within the basal ganglia leading to the hallmark motor symptoms of PD: tremor, bradykinesia/akinesia, rigidity, and postural instability.[1] To counteract the deleterious effect of dopamine depletion, dopamine replacement therapy is usually initiated in the early stages of the disease. However, neurophysiological alterations related to disease progression and prolonged use of dopaminergic agents often leads to drug-induced dyskinesia. Within 5 years of dopamine replacement therapy initiation (levodopa), 30–50% of patients report experiencing dyskinesia;[2,3] by Year 10 of treatment, 60–100% of patients report dyskinesia.[2,4] Although there are different manifestations of dyskinesia, the most common type of drug-induced dyskinesia in PD is choreic peak-dose dyskinesia.[5] Dyskinesias are characterised by random, non-rhythmic (in appearance), and unsustained involuntary movements that can be present throughout the body.[6] Dyskinesia can lead to diminished quality of life for both patients and their caregivers, and create an additional burden on the healthcare system. Several approaches may be undertaken by clinicians to control dyskinesia while maintaining clinically significant reductions in typical PD symptoms. In this paper, we first provide

an overview of the current approaches in managing dyskinesia. We then discuss a novel approach to the management of dyskinesia that we have recently put forward, how this approach could improve the quality of life of patients, and how it could be implemented within practice.

CURRENT APPROACH

Many clinicians treating a PD patient exhibiting dyskinesias will promptly attempt to reduce their amplitude using one of the following approaches:

Modification of Dopamine Medication Titration

While the primary option for management of dyskinesia is to reduce medication dosage, this can lead to the resurgence of parkinsonian symptoms. Hence, this option is not viable for many patients as most prefer to experience mild dyskinesia than to become 'immobilised' by their symptoms. Another option available to clinicians is the fractionation of medication doses. This method maintains the overall daily dose of medication by having patients take smaller doses of medication at shorter intervals during the day. The theory behind this approach is to reduce the pulsatile nature of medication intake resulting in more stable levels of dopamine within the system. However, this method often provides adequate management of dyskinesia for a limited time only and is effective in only some patients. This has led some to try controlled-release formulations of medication.[7] While this in theory could help in the management of dyskinesia by further reducing the pulsatile nature of medication intake, very little scientific evidence supports its use in clinical practice.[8]

Dopamine Agonists

Another option available to clinicians is the co-administration of dopamine agonists.[9] The idea behind this approach is to provide relatively low doses of both medications thus minimising the possible occurrence of side effects. However, the effectiveness of such an approach in reducing dyskinesia is very sparse at best.[8] Additionally, dopamine agonists are associated with more non-motor side effects than levodopa and it has been previously shown that some patients on dopamine agonist monotherapy can also develop dyskinesia.[10]

Continuous Drug Delivery (Duopa™/Duodopa; Apomorphine)

Building on the theory that reducing the pulsatile delivery of medication will minimise dyskinesia, continuous drug delivery systems such as duodenal infusion of levodopa have been developed. Previous studies have demonstrated the efficacy of this approach in reducing the duration of dyskinesia.[11,12] Similarly, continuous subcutaneous apomorphine infusion has been shown to significantly reduce dyskinesia.[13] These approaches however require a complex procedure and extensive long-term monitoring to limit the potentially severe complications. As such, this treatment option may not be suitable for many patients and may indeed add to the burden faced by patients and their caregivers.

Amantadine

Since previous studies have demonstrated a link between the overexpression of N-methyl-D-aspartate (NMDA) receptors and dyskinesia, another option available to clinicians is to provide adjunctive NMDA antagonist medications to patients. According to the European Federation of Neurological Societies (EFNS) guidelines, amantadine (200–400 mg/day) has a Level A recommendation for the management of levodopa-induced dyskinesia.[14] Amantadine has been shown to significantly reduce the duration of dyskinesia[15] while simultaneously providing a mild anti-parkinsonian effect.[16] However, many patients' response to amantadine is fleeting and thus its use provides only temporary relief. Recently, an extended release formulation of amantadine has been introduced and shown to be effective with minimal side effects at a daily dose of 340 mg.[17]

Serotoninergic Agents

Given the close relationship between the dopaminergic and serotoninergic systems within the basal ganglia, there have been some investigations into the use of serotoninergic medication to control dyskinesia. Clozapine, a high-affinity serotoninergic agonist, was shown to significantly reduce dyskinesia.[18] However, its severe side effect profile requires intensive monitoring thus greatly limiting its use. Many preclinical studies targeting the serotoninergic system yielded promising results, however clinical trials assessing the efficacy of 5-HT_{1A} receptor antagonists such as buspirone[19-21] or sarizotan[22] failed to demonstrate an improvement of levodopa-induced dyskinesia and even led to the worsening of parkinsonian symptoms.[23] Nonetheless, there is currently an ongoing clinical trial of buspirone for the management of dyskinesia (NCT02617017). To optimise the efficacy of this treatment strategy, a current

clinical trial is examining the use of combined buspirone and amantadine for the management of levodopa-induced dyskinesia (NCT02589340). Other serotoninergic agents such as fluoxetine[24] have also been shown to be moderately effective in managing dyskinesia. More recent observations encourage the use of combined 5-HT_{1A} and 5-HT_{1B} receptor antagonists, such as eltoprazine, and suggest the use of serotonin transporter (SERT) inhibitors as an alternative target.[25]

Surgical Interventions

In severe cases where dyskinesias are refractory to drug management, surgical options may be considered. Deep brain stimulation of the globus pallidus internus and subthalamic nucleus have been demonstrated to significantly reduce dyskinesia by ≥80%.[26,27] While some of this improvement may be linked to a reduction in medication dosage after surgery, electrical stimulation of these targets is thought to induce antidyskinetic mechanisms. However, several restrictions associated with age, cognition, and psychiatric symptoms limit the use of these interventions. Lesions of the globus pallidus internus and subthalamic nucleus have also been shown to significantly improve drug-refractory dyskinesia.[28,29] Yet lesions may only provide unilateral dyskinesia alleviation, as bilateral procedures are associated with significant complications.

CLINICAL QUANDARY

While the aforementioned interventions can provide a variable degree of reduction in dyskinesia amplitude and duration, one question clinicians should be asking themselves is whether it is always a necessity to treat dyskinesia. Previous studies have demonstrated that dyskinesia may not be related to quality of life in PD.[2,30-32] This may be because dyskinesias do not affect every patient in the same way. It was recently proposed that the decision to treat should not be based on the presence or absence of dyskinesia but rather on the impact on the motor repertoire available to patients.[5] This idea stemmed from several studies demonstrating that dyskinesia and other motor symptoms of PD did not impair the performance of every type of voluntary movement. In other words, the impact of dyskinesia was closely related to the amplitude and velocity of the task being performed. As such, dyskinesias will have a deleterious effect on patients' quality of life only if their motor repertoire (the activities that they usually perform daily) is altered by the condition. Since not every person requires the same motor repertoire in their daily life, the decision to treat would need to be personalised to each patient. For instance, a seamstress required to perform very fine movements for her daily occupations may require a change in treatment to manage even very mild dyskinesia despite good alleviation of parkinsonian symptoms (Figure 1, Case 1). Conversely, a patient whose dyskinesia does not interfere with his/her daily activities, because they mainly involve gross motor tasks or because the dyskinesias occur at a time of day when fine motor movements are not as essential, may not require immediate changes to his/her treatment regimen that otherwise satisfactorily manages his/her symptoms (Figure 1, Case 2).

One of the main issues with such an approach is that clinicians can only observe dyskinesia during a very narrow time window when patients are in the clinic. They must then rely on patient reports which are highly unreliable as their perception can be altered due to the disease. We have observed patients reporting no dyskinesia whilst exhibiting constant dyskinesia lasting several hours when they visited the laboratory; this has been presented on multiple occasions. Conversely, we have also observed patients that have communicated having severe impairments due to dyskinesia and exhibited no involuntary movements throughout several 4 to 5-hour monitoring periods. Therefore, new evaluation methods need to be implemented to capture the changes in motor repertoire and identify whether they are detrimental to patients' quality of life (Figure 2).

WHAT WOULD BE THE BENEFITS OF SUCH AN APPROACH?

Quality of Life

The impact of dyskinesia on quality of life is still being debated. For instance, a recent study by Hechtner et al.[33] found that dyskinesia, whether peak-dose or biphasic, did not have a significant impact on quality of life as assessed by the 39 item Parkinson's Disease Questionnaire (PDQ-39)[34] and EuroQol five dimensions questionnaire (EQ-5D)[35] criteria. Similarly, Martínez-Martin et al.[36] found that motor complications such as dyskinesia, as assessed by the Movement Disorder Society-Unified Parkinson's Disease Rating Scale (MDS-UPDRS) Part IV,[37] did not exhibit a significant influence on health-related quality of life. Fereshtehnejad et al.[38] also did not observe any significant influence of

dyskinesia on quality of life. On the other hand, Soh et al.[39] have observed that impairments in motor function, as assessed by the MDS-UPDRS Part IV,[40] contributed directly to health-related quality of life as well as indirectly through limitations in self-care. Likewise, Wu et al.[41] observed that motor complications such as dyskinesia had a significant impact on quality of life. Specifically, they demonstrated that motor complications were a significant, albeit minor, determinant of the PDQ-3934 summary index as well as the activities of daily living.

So why is it that some studies find that dyskinesia are detrimental to the quality of life of patients with PD, while others do not? It is possible that this may stem from the clinical characteristics of the sample populations. Some studies, such as that from Martínez-Martin et al.,[36] had participants with very little dyskinesia. It is therefore more likely that the dyskinesias do not interfere with their quality of life at a group level. On the other hand, it may also be that in other studies where dyskinesias have been shown to have a deleterious effect on quality of life, it was through an indirect path. For instance, Soh et al.[39] and Wu et al.[41] both observed that dyskinesia had a negative effect on activities of daily living. More specifically, Hechtner et al.[33] observed that peak-dose dyskinesia had a significantly negative impact on activities of daily living. This is in direct relation to our proposed approach, where treatment should be based on the impact of dyskinesia on the motor repertoire of patients. In Case 1, the daily activities of the patient are hampered by the presence of dyskinesia. As such, this would inextricably lead to a reduction in quality of life. In Case 2 however, the presence of dyskinesia does not affect the motor repertoire of the patient. As such, his/her quality of life would also not be affected. Soh et al.[39] demonstrated that limitations in performing activities of daily living was one of the strongest contributing factors to diminished health-related quality of life. Similarly, Fereshtehnejad et al.[38] demonstrated a significant influence on the activities of daily living as assessed by the MDS-UPDRS Part II,[40] on the summary index of the PDQ-3934 (overall quality of life), but also on specific domains of quality of life such as mobility, activities of daily living, stigma, social support, cognition, and communication domains. By only modifying the drug regimen of patients whose motor repertoire is altered we may be able to optimise the improvement in quality of life concomitantly, minimising the burden associated with the titration period of new medication that may temporarily negatively impact the quality of life of patients.

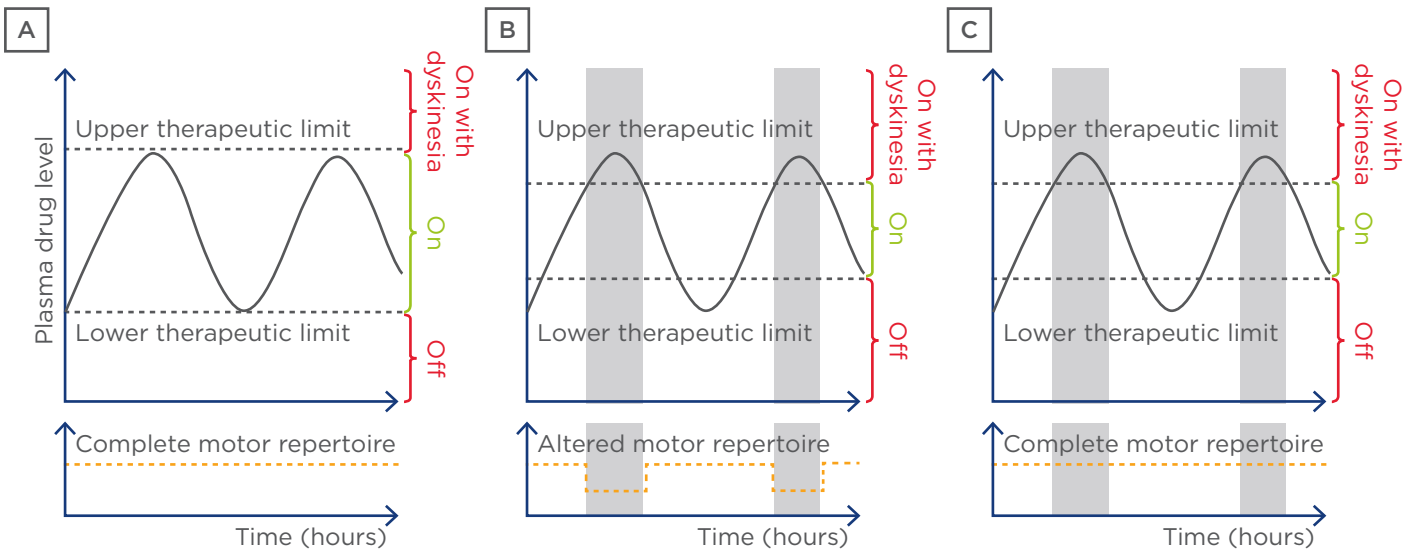

Figure 1: Graphical representations of various contexts of levodopa plasma fluctuations.
A) Honeymoon period: Fluctuations in levodopa plasma level from the onset of treatment, and the motor repertoire available to patients. B) Case 1: Short-term variations in levodopa plasma levels associated with motor fluctuations, and changes in motor repertoire as the therapeutic window narrows. C) Case 2: Short-term variations in levodopa plasma levels associated with motor fluctuations but without any changes in motor repertoire as the therapeutic window narrows.

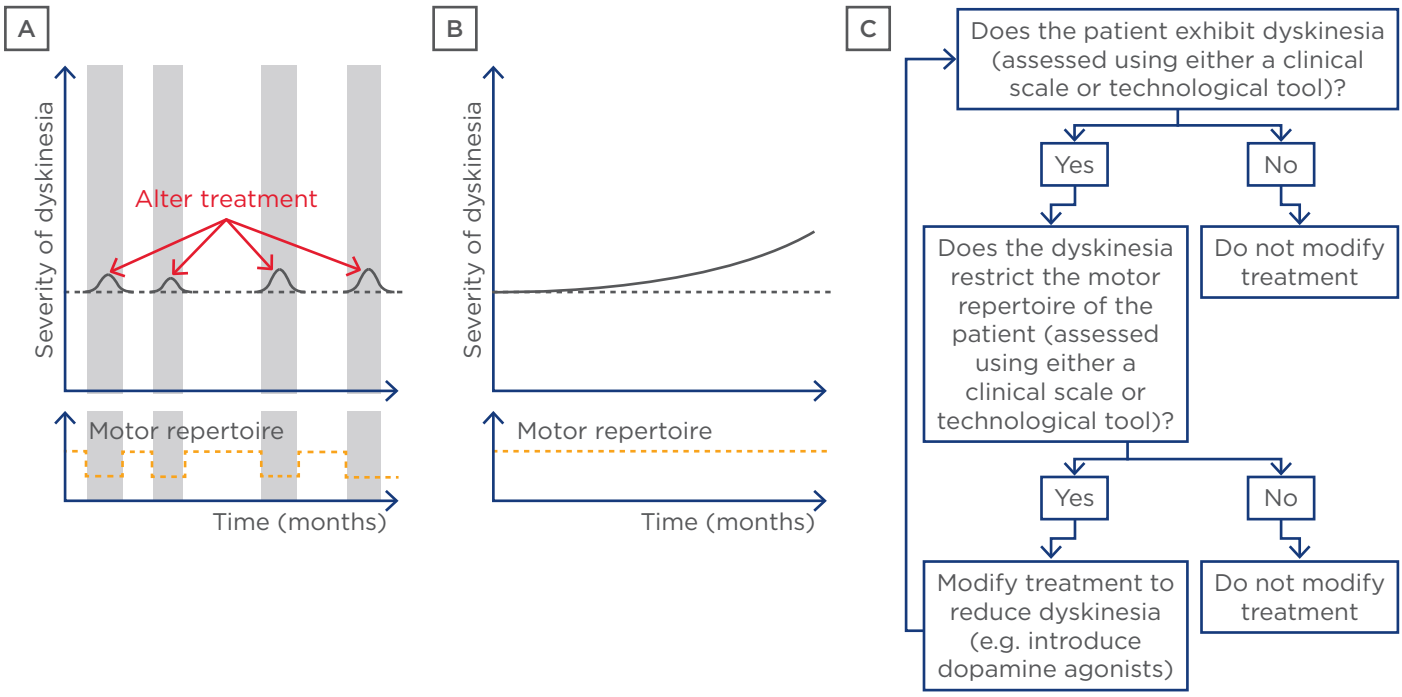

Figure 2: Graphical representation of the long-term variations in the severity of dyskinesia.
A) Case 1: Long-term variations associated with alterations in motor repertoire that warrant a change in treatment. B) Case 2: Graphical representation of the long-term changes in dyskinesia severity that does not alter the motor repertoire and thus does not require a modification in therapy. C) Proposed decision algorithm for the management of dyskinesia.

Caregiver Burden

Few studies have examined the impact of dyskinesia on caregiver burden. Some have observed that the presence of dyskinesia or motor complications were not associated with an increased caregiver burden. Agrawal et al.[42] observed that although there was a very mild significant correlation between dyskinesia and caregiver quality of life, dyskinesias were not a significant predictor of caregiver burden or quality of life. Oguh et al.[43] observed, in a large cohort of >2,000 caregivers of patients with PD, that those exhibiting more severe strain were caring for patients with PD that had a higher incidence of motor fluctuations. However, in a regression analysis, motor complications were not a significant predictor of caregiver strain. Leroi et al.[44] observed that motor complications, as assessed by the MDS-UPDRS Part IV, were not significant predictors of caregiver quality of life. On the other hand, Martínez-Martin et al.[45] observed that motor complications, combined with disease duration and disability, were significantly related to caregiver burden, anxiety, and depression. Similarly, Ozdilek and Gunal[46] demonstrated that caregiver burden was significantly affected by the presence of dyskinesia and their impact, as assessed by the MDS-UPDRS Part IV. As such, it seems that the presence of dyskinesia variably impacts quality of life and may not be a very strong predictor of caregiver burden. However, functional limitations in activities of daily living seem to consistently play an important role in caregiver burden. Ozdilek and Gunal[46] also observed that caregiver burden was significantly associated with impairments in activities of daily living of PD patients, as assessed by the MDS-UPDRS Part II. In a meta-analysis, Lau and Au[47] demonstrated that the significant impact of functional limitation in activities of daily living on caregiver burden was greater than that of mood problems and cognitive impairment.

Taken together, this indicates that limitations in activities of daily living, rather than the mere presence of dyskinesia, is of greater importance to the quality of life of patients and their caregivers. Implementing changes to treatment regimens based on the impact of dyskinesia on activities of daily living, comprising the entire motor repertoire of patients with PD, may therefore lead to better quality of life of both patients and their caregivers, as well as alleviating caregiver burden.

HOW COULD THE PROPOSED APPROACH BE IMPLEMENTED?

The most common approach to assessing dyskinesia in patients with PD is to use clinical scales. Several scales are available to clinicians to assess dyskinesia (Table 1). For instance, Part IV of the MDS-UPDRS[37] contains two questions related to the frequency and impact of dyskinesia. Other scales are entirely dedicated to the evaluation of dyskinesia in PD. The Abnormal Involuntary Movement Scale (AIMS)[48] assesses limb-specific location of dyskinesias as well as their intensity. The Unified Dyskinesia Rating Scale (UDysRS)[49] and the Rush Dyskinesia Rating Scale (RDRS)[50] both objectively assess the impact of dyskinesia on activities of daily living. The UDysRS also reports patients' perception of the impact of their dyskinesia. The Lang-Fahn Activities of Daily Living Dyskinesia Scale (LFADLDS)[51] and the Parkinson Disease Dyskinesia Scale (PDYS-26)[52] also report patients' perceptions relating to the impact of dyskinesia on specific daily activities. Interestingly, a recent study demonstrated that measures comprising patients' perception (i.e. UDysRS, LFADLDS, and PDYS-26) detected an effect of treatment with amantadine while the MDS-UPDRS-IV, AIMS, and RDRS did not.[53] Furthermore, Goetz et al.[53] observed that the UDysRS provided the largest effect size, indicating that the combination of objective measures of dyskinesia and subjective patient perceptions could best capture the impact of changes in treatment. Utilising scales that examine the impact of dyskinesia on activities of daily living, both objectively and subjectively, may lead to better treatment decisions for patients with PD. Although the scales mentioned previously can provide the impact of dyskinesia on common activities of daily living, they may not cover the entire motor repertoire of patients with PD. As such, the development of new scales, or amendment of currently used scales, may provide even better information to decide when a change in treatment should be explored to manage dyskinesia. For instance, adding elements to current scales that relate to a more complete motor repertoire and that include components similar to those observed in for example the Motor Activity Log (MAL),[54] where both quantity and quality of movements are assessed simultaneously, may provide a better picture of the overall impact of the dyskinesia and indicate whether a change in treatment strategy is warranted.

Finally, recent advances in wearable technology enable low-cost, unobtrusive data collection spanning several hours to days. In combination with advanced mathematical analytics, this technology can identify dyskinesia during specific tasks[55-58] and even within uncontrolled ambulatory settings.[59-61] While more work is required to implement the use of wearable technology in clinical practice, this technology may soon help inform clinicians about the duration and severity of dyskinesia within the patients' living environment as well as the impact on patients' motor repertoire. For example, instead of patients taking their medication at predefined intervals, data collected from body-worn sensors may be used to indicate when patients should take their medication based on the longitudinal monitoring of their motor behaviour.

Table 1: Characteristics of the dyskinesia rating scales.

	Evaluation	Time to complete (years)	Type	Specific to dyskinesia	Assessment period
MDS-UPDRS IV	Frequency + Impact	5	SR	Yes	1 week
AIMS	Limb-specific severity	15	C	No	During visit
UDysRS	Impact on ADL	15	SR + C	Yes	1 week
RDRS	Severity during ADL	5	C	Yes	During visit
LFADLDS	Disability during ADL	5	SR	Yes	A few days
PDYS-26	Impact on ADL	10	SR	Yes	1 week

MDS-UPDRS IV: Movement Disorder Society-Unified Parkinson's Disease Rating Scale Part IV; AIMS: Abnormal Involuntary Movement Scale; UDysRS: Unified Dyskinesia Rating Scale; RDRS: Rush Dyskinesia Rating Scale; LFADLDS: Lang-Fahn Activities of Daily Living Dyskinesia Scale; PDYS-26: Parkinson Disease Dyskinesia Scale; ADL: activities of daily living; SR: self-report; C: clinical evaluation.

Feedback could be provided through a simple smartphone application. This may optimise responses as well as reduce motor fluctuations, such as those caused by dyskinesia. This will enable physicians to personalise treatments on a patient-specific basis.

CONCLUSION

As the management of motor symptoms of PD leads to motor complications such as dyskinesia, there is a need to ask whether these complications need to be controlled at all costs in every patient. The shift towards personalised medicine should also be applied in the management of drug-induced dyskinesia. Rather than modifying a treatment approach that is otherwise efficacious in managing motor symptoms, the decision to address dyskinesia by modifying the treatment regimen should be based on the impact of dyskinesia on the motor repertoire of patients and not solely on its presence. We believe that this will improve the quality of life for patients in the long-term, lessen caregiver burden, and alleviate some of the financial burden on the healthcare system. To adequately implement such an approach, there needs to be further developments in how patients are evaluated. Whether it is through the development of new or amended clinical scales, or the use of wearable technology to monitor patient symptoms in their natural environment, collaborative work between clinicians, engineers, and scientists will enable us to move forward more quickly in personalising care and improving the quality of life for patients with PD.

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OCCUPATIONAL ALLERGIES: A BRIEF REVIEW

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ABSTRACT

Occupational allergies are groups of work-related disorders that are accompanied by immunologic reaction to workplace allergens and include occupational asthma, rhinitis, hypersensitivity pneumonitis, dermatitis, and anaphylaxis. This mini review presents a brief analysis of the more important aspects of occupational allergic disorders.

Keywords: Occupational allergies, asthma, rhinitis, dermatitis, hypersensitivity pneumonitis, anaphylaxis.

INTRODUCTION

The epidemiologic features of diseases have changed since the industrialisation and civilisation of modern society, particularly in the second half of the 20th century. The significant increase in prevalence and diversity of occupational allergies (i.e. occupational asthma [OA], rhinitis, dermatitis, hypersensitivity pneumonitis, and anaphylaxis) is part of this alteration, in both developed and developing countries.[1] Occupational allergy should be considered a real challenge, therefore early detection is highly recommended. Missed or untreated occupational allergy, either by workers or employers, may lead to continuous exposure, progressive health problems, and worsening of the medical condition. Consequently, mild-to-severe medical injuries or pathologic conditions, together with job loss and economic burden, could occur.[2]

Usually, the entire body of a worker with a certain genetic background is affected by allergens in the workplace. Skin and respiratory systems, the first exposed organs, are the most frequent roots of occupational exposure, which may cause local or systemic allergic (immunologic) disorders. On the other hand, it is demonstrated that skin exposure may result in respiratory reaction and vice versa.[3] Therefore, occupational allergies in both skin and respiratory systems should be considered jointly.

OCCUPATIONAL ASTHMA

Definition

According to the American College of Chest Physicians (ACCP) consensus statement, every occupation-related asthma is classified under the broad term of work-related asthma (WRA), which includes: OA (*de novo* asthma induced by exposure in the workplace) and work-exacerbated asthma (WEA; aggravation of pre-existing or concurrent asthma due to work-related factors, such as aeroallergens, irritants, or exercise). OA includes sensitiser-induced asthma (asthma associated with immunologic and allergic mechanism) and irritant-induced asthma (which occurs due to aspiration of a great amount of an irritant material in the workplace) (Table 1).[2,4-6]

Although the distinction between OA and WEA may be very difficult, it is of paramount importance due to the differences in treatment, prognosis, and legal aspects.[7] The coexistence of OA and WEA in a patient could be confusing. In patients with history of well-controlled childhood or long-past asthma, the onset of asthma following workplace exposures is classified as new onset OA rather than WEA. Meanwhile the recurrence of asthma after non-occupational exposures is considered as WEA.[4]

Table 1: The classification of work-related asthma.[2,4,6]

Work-related asthma
Occupational asthma - Sensitiser-induced asthma (allergic) - Irritant-induced asthma (non-allergic)
Work-exacerbated asthma

History

Since the 18th century, physicians have explored the association of certain trades with progression of respiratory symptoms. The list of asthma causative or triggering factors in workplaces was developed further during the 20th century, especially by the mid-1980s, resulting in hundreds of distinct causes of OA being recognised thus far.[4]

Epidemiology

WRA is the most common type of occupational pulmonary involvement.[8] Although its prevalence has not been reported definitely, it is estimated that up to 25% of adult asthma patients have WRA.[4,9] On the other hand, it is believed that attributable risk of OA in adult asthma is nearly 15%. Higher prevalence is seen in individuals exposed to chemicals (e.g. painters, welders, etc.), animal handlers, woodworkers, cleaners, healthcare workers (9% of cases), those working in food processing, and so on.[2,10-12] Conversely, some studies showed no increase, or even decrease, in the prevalence of respiratory allergies in farming and textile industries, consistent with the so-called 'hygiene hypothesis'.[13,14] Well-recognised high WRA risk groups are females, smokers, those with history of upper airway symptoms and bronchial hyper-responsiveness, and those with certain hereditary factors, atopic histories, and frequent exposure to high amounts of causative factors.[2,5]

Pathophysiology and Causative Agents

The disease is induced by the interaction of multiple intrinsic (i.e. genetics) and extrinsic (i.e. environmental) factors, similar to other non-communicable chronic diseases. Therefore, new discoveries in the fields of molecular pathology and genetics, along with prevention of exposure to environmental causative agents, has markedly decreased the prevalence of WRA.[2,9] The increasing list of known causative factors of WRA (>400) contains both high molecular weight (HMW) antigens (i.e. biologically derived substances >10 kDa such as the proteins and glycopeptides produced by animals, plants microbes, etc.) and low molecular weight (LMW) antigens (such as chemicals and metals). Although HMW antigens were the most common cause of conventional OA, the role of LMW antigens has been emphasised recently.[2,4,9,15] WRA occurs through the immunoglobulin E (IgE)-mediated reaction to HMW antigens. Meanwhile, the LMW antigens work either as haptens to provoke immunologic reaction, or via an unknown mechanism.[9]

Diagnosis

WRA is diagnosed based on a confirmed asthma diagnosis plus evidence of workplace exposure worsening symptoms. Early diagnosis is an advantage for patients. Generally, there are limited standardised tests for workplace antigens. Thus, OA diagnosis is not based on straight forward laboratory tests.[9] Taking complete medical histories, performing physical examinations, appropriate imaging, and laboratory tests, together with clinical impressions of WRA, are the key points for diagnoses.[16] Questionnaires are only acceptable when used as screening tools because of their lack of specificity. The standard pulmonary tests detecting increased airway hyper-reactivity associated with occupations would be useful diagnostic tools. Meanwhile, the high sensitivity and specificity of daily, continuous peak flow evaluation has proven the most useful method. The specific antigen inhalation challenge test is the gold standard for diagnosis of sensitiser-induced asthma and detection of new antigens. In general, it is not a requisite test because of potential risks, possible false positive and negative results, and requirement of highly specialised equipment; particularly when other methods can be used. Immunologic tests can be used to identify HMW antigens in sensitiser-induced asthma;[2,5,17] specific IgE and skin-prick testing are highly recommended in this regard.[18] Meanwhile, detection of specific IgE against HMW antigens is not commonly available.[2] Evidence shows that component-resolved diagnostics may be used to clarify the allergens (e.g. in baker's asthma),[19] thus development of a protocol for component-resolved diagnostics usage was attempted.[20] Unfortunately, despite these efforts, no ideal biomarker has been found yet.[17] To avoid unnecessary asthma treatment, OA diagnosis should be differentiated from work-associated irritable larynx syndrome, which is actually laryngeal irritation induced by exposure to LMW irritants in workplaces.[21,22]

Management

Patient quality of life can be severely affected by WRA, and depression and anxiety incidence in individual WRA is about 50%, which is more common than in asthma. Thus, treatment should be considered seriously.[9] The mainstay of every policy in WRA management is early reduction or eradication of exposure factors if possible.[2] This is the main reason to distinguish WRA from non-OA.[23] Furthermore, medical treatment of WRA should be conducted according to asthma guidelines. It should be noted that drug treatment should be accompanied with exposure avoidance. However, in WEA or irritant-induced asthma, patients could return to the same role in an exposure-free environment following asthma control.[2,23] The antigen-specific immunotherapy may be effective in sensitiser-induced asthma with known causative agents.[24] Prognosis is determined by early diagnosis, removal of exposures, patient age, respiratory function at the time of diagnosis, and exposure duration. However, several years of exposure avoidance and medical management are usually required before judgement may be made on a complete cure.[2,6]

Prevention

As the primary prevention, the first step is to remove all causative factors from a workplace.[25] If this is not applicable, use of less irritating alternatives in addition to provision of good personal protection and appropriate ventilation may be beneficial. Pre-employment medical work-ups are not always diagnostic. As secondary and tertiary prevention, periodical workplace inspection, and medical check-ups and treatment by occupational and pulmonary physicians will be useful.[2,25]

OCCUPATIONAL ALLERGIC RHINITIS

Definition

Occupational allergic rhinitis (OAR) is characterised by induction or worsening of IgE-mediated sneezing, watery rhinorrhoea, and nasal congestion, due to inhaled exposure to work-derived agents.[2] These symptoms may be intermittent or persistent following a latency period after exposure.[26,27] In contrast, non-allergic rhinitis has no immunologic bases or latency period and may be seen just after a single high-dose exposure.[28]

Epidemiology

The prevalence range of OAR has been reported at 0.2–18% in the general population[2,26] and at 2–87% of exposed workers.[27] It is believed that OAR is underestimated and underdiagnosed, but is still more frequent than OA.[26] Up to 90% of asthmatics suffer from rhinitis while only one-third of rhinitis cases have concomitant asthma.[29] Changes to work environment and subsequently to allergic factors may change the epidemiology of OAR.[2]

Causative Agents

Similar to other allergic conditions, hundreds of causative factors have so far been recognised for OAR.[15,28] HMW mould, animal or plant derivatives, and LMW chemical substances (such as haptens) in workplaces may induce OAR.[2,29,30] OAR is more prevalent in bakers, kitchen workers, waste collectors, cleaners, healthcare staff, hairdressers, and agricultural and textile industry workers.[26,29,31,32]

Mechanisms

Genetic backgrounds are considered to be substantial factors in the occurrence of asthma and allergy,[33-35] and it is reasonable to postulate that genetic predisposition may lead to OAR, due to IgE-mediated immunologic reaction to allergens.[2,27] This reaction includes Type I (IgE-mediated) hypersensitivity reaction, while Types III and IV may also occur. The classification and severity of OAR is important for selecting treatment options.[2]

Diagnosis

Identification of allergic factors is not easy, but could be achieved with an exact medical history, immunologic examination, and nasal mucosa tests. Although detection of nasal-specific IgEs against chemical allergens is useful for specific diagnosis, it is not feasible in many centres. Meanwhile, the nasal provocation test for allergens is highly valuable for diagnosis confirmation.[2,26]

Management

OAR interferes with personal life and induces personal restrictions, decreased productivity, and work disruption. Furthermore, continuous exposure to workplace allergens could progress OAR to WRA and more severe forms of airway involvements. Therefore, allergen exposure avoidance together with the appropriate drug therapy is the best treatment approach. Immunotherapy and

surgical therapy (in some cases) could also be effective.[2,36]

Prevention

Similar to occupational asthma, three levels of prevention may be used for OAR.[25] The highest priority is early detection and elimination of allergens in the workplace. It may be performed using policies such as substitution with alternative non-allergen substances, or complete elimination of allergens and appropriate ventilation, although the latter is less effective. Respiratory protective tools, such as masks, may reduce the allergen dose, but protection quality depends on specification and qualification of the mask and the size and type of allergens. The pre-employment evaluation of workplaces may not be always effective in allergen prevention, but continuous education of employers and employees is more useful.[2]

OCCUPATIONAL HYPERSENSITIVE PNEUMONITIS

Identification and Classification

As a complex syndrome, occupational hypersensitive pneumonitis (OHP) occurs following repetitive exposure and inhalation of a wide variety of sufficiently small (<5 μm) organic particles in the workplace. These particles can reach alveoli and provoke an exaggerated immune response of small airways, parenchyma, and pulmonary alveoli. The causative particles may be derived from excretory substances and animal body constituents, floating fungi and bacteria, protozoa, insect proteins, and LMW organic or inorganic chemical compounds.[2,37] Based on symptoms and type of onset, OHP can be classified as acute, subacute, or chronic.[2,38] However, as classifications overlap, cluster analysis has suggested a division of these classifications into two clusters.[16,39]

Epidemiology

Generally, the prevalence of OHP varies in different conditions,[38] however pneumonitis is more prevalent in the regions and time periods with higher probability of exposure to causative factors. Following higher detection of OHP, diagnosis rates are increasing. As previously mentioned, accurate estimation of epidemiologic features of OHP is difficult because OHP is influenced by the type of causative factors and the nature of exposure.[2] The severity, duration, and frequency of exposure are considered as extrinsic risk factors of OHP. Thus far, no demographic or genetic risk factors have been discovered.[2,40] The mortality rate of OHP is low, particularly in females and non-elderly people, but increases in chronic forms which are mostly accompanied by pulmonary fibrosis.[2,41]

Causative Agents

Aetiology, natural history, and pathogenesis of OHP are not well described in current publications.[40] However, it has been recognised that important causative antigens (i.e. proteins and chemicals) are: plant powder and dust, animal body constituents and excretory substances, insects, fungi, bacteria, drugs, organic chemicals, and so on. It is also believed that LMW chemicals (such as zinc, inks, dyes, and isocyanates, etc.) and especially metal-working fluids are increasingly causing OHP.[2,8,16,42,43] Other studies showed that contamination with micro-organisms (e.g. *Pseudomonas fluorescens*, mycobacteria, and fungi) could also be the cause of OHP in some cases.[43-45]

Diagnosis

Despite valuable efforts by researchers, there are no definite diagnostic criteria for OHP.[43] Therefore, a detailed medical history and physical examination together with an occupational history are the most important steps to diagnose OHP. In addition, for definitive diagnosis, pathological confirmation is not always mandatory. Meanwhile, chest imaging, pulmonary function tests, bronchoalveolar lavage, and transbronchial lung biopsy may be helpful for diagnosis. Some tests are available to detect causative antigens, such as antigen-specific antibody titration, lymphocyte proliferation test (by antigen addition), the environmental challenge test, and precipitation antibody test. The antigen inhalation challenge test is valuable in antigen identification, and it may also detect OHP exacerbation. OHP should be differentiated from other interstitial lung diseases such as idiopathic interstitial pneumonitis, chronic obstructive pulmonary disease, and WRA.[2,38]

Management and Prognosis

Avoiding exposure to causative factors is the first necessary step, even in under-treated patients, because the pathologic condition may progress. In mild cases, antigen avoidance may provide suitable prognosis, but in intermediate-to-severe, acute, or chronic cases, a corticosteroid prescription of prednisolone is used as a symptomatic therapy. The prognosis is poor in cases with continuous

antigen exposure or chronic fibrotic changes, with weak response to treatment.[2,46]

Prevention

Complete elimination of the causative antigen in the workplace is mandatory; therefore, it is highly recommended that patients change to a safer work environment with fewer causative substances. Nevertheless, appropriate workplace ventilation and application of protective dust or gas masks may also be effective in exposure reduction. Furthermore, worker and employer education on OHP symptoms, avoidance of causative factors, protection methods, and so on may be beneficial.[2]

OCCUPATIONAL SKIN ALLERGIES

Definition and Classification

Skin exposure to workplace agents may result in immune mediated, non-immune mediated, and systemic effects.[3] Workplace-related skin diseases are defined under the general term of occupational skin diseases (OSD) which may be further classified into many categories, such as dermatitis, urticaria, different injuries, infection, insect bites, etc.[2] Occupational skin allergies (OSAs) including dermatitis and urticaria are OSDs due to immunologic reactions. In this way, occupational allergic dermatitis is defined as a local sensitisation reaction of the skin, based on an immunologic mechanism. On the other hand, occupational irritant dermatitis is a non-immunologic local reaction of skin as a result of exposure to workplace irritants. Similarly, urticaria, with apparent relation to workplace causative factors, is occupational.[2]

Epidemiology

As the most frequent occupational disease, the estimated OSD annual costs exceed $1 billion worldwide.[47,48] Because of direct or indirect contact of the widespread skin surface area with as many as 10,000 allergic agents, OSDs are commonly observed in different workplaces and occupations. Due to the differential nature of OSDs, epidemiologic studies are unable to provide accurate data and evaluation.[2] Recent studies indicated a decline in occupational dermatitis incidence in most European countries.[47] OSA prevalence is different in each sex but nonetheless accounts for nearly 90–95% of OSDs.[3,47] OSA is observed most commonly in personal service workers, including beauticians, hairdressers, and healthcare workers, as well as in food processing industries, bread makers, chefs, agricultural workers, etc.[2,47]

Causative Agents

Although the causative factors of OSAs are numerous, the most frequent are metals (nickel, chrome, etc.) and metal-working fluids, epoxy and acrylic resins, rubber, agrichemicals, cutting oil, cleansers, and some medications and plants. In addition, the main causative allergens of occupational urticaria include organic derivatives of food, plants, animals, wheat, crops, natural rubber products, etc.[2,42,47] On the other hand, chemical burns from acids, alkalis, hydrogen fluoride, cement, heating oil, etc. usually induce more severe types of acute irritant dermatitis.[2]

Proteins are frequently the causative allergen for recurrent allergic dermatitis, through different pathogenesis from Type IV allergic dermatitis, called occupational protein-contact dermatitis. Furthermore, some believe that hydrolysed wheat powder in soaps and shampoos may result in percutaneous-mucosal sensitisation and life-threatening wheat allergy. As an additive to cosmetics, foods, and drinks, the presence of the cochineal pigment may cause immediate acute allergy reactions.[2]

Diagnosis

Occupational urticaria and dermatitis mostly occur on open skin areas i.e. hands, upper arms, and the face.[2] Diagnoses are based on accurate medical history, physical examination, and patch tests such as the simple closure test, open test, photopatch test, and repeated open application test. The patch tests evaluate the irritability of agents or identify the causative factors of allergic contact dermatitis.[2,47] To diagnose occupational urticaria, the prick test is highly sensitive and specific. The allergen-specific IgE may also be a useful criterion.[2] In recent times, it has been recommended to consider both skin and respiratory involvement in occupational allergic comorbidity.[47]

Management

The identification and complete elimination or avoidance of the allergens and irritants is the most important priority in prevention and treatment. As the comorbidity of urticaria and dermatitis is presumable, it is required to alleviate the symptoms of both. Antihistamine prescriptions, topical or systemic steroids, immune suppressors, and ultraviolet phototherapy are useful treatments.

However, by eradication of the causative factor, the allergic dermatitis may be substantially cured.[2]

Prevention

The primary prevention method is training, to improve the knowledge and awareness of workers and employers.[47,49] Meanwhile, the application of moisturising agents, barrier-creams, and non-allergenic gloves, masks, and clothes are recommended.[2]

OCCUPATIONAL ANAPHYLAXIS

Definition and Epidemiology

The occurrence or worsening of anaphylactic attacks due to workplace exposure to causative antigens is defined as occupational anaphylaxis (OAn).[50] The incidence rate of OAn is estimated to be 0.05–2% worldwide, and is thought to be increasing.[2]

Diagnosis

Occasionally, late-onset anaphylaxis in the workplace may be caused by non-occupational allergens (ingestion-related) and should be differentiated from OAn, thus exact history-taking and clinical evaluation constitute an anaphylaxis diagnosis.[50,51]

Causative Agents

Theoretically, every HMW and LMW allergen that triggers OA or urticaria may cause OAn. Natural rubber latex exposure and bee or wasp stings are the major causes of OAn, however workplace exposure to some medications, foods, insects, mammal and snake toxins, and chemicals are also notable.[50,51]

Anaphylaxis by Bee or Wasp Stings

Anaphylaxis due to bee or wasp stings is seen mostly in apiculture, agriculture, forest, and landscaping industries, etc. Diagnosis is based mainly on medical and environmental history. The presence of atopy history in employees increases risk of bee or wasp anaphylaxis. Prevention can involve suitable protection tools. Similar to other anaphylaxes, adrenaline self-injection kits and antigen-specific immune therapy are effective treatments and should be prepared.[50,51]

Anaphylaxis by Latex

Natural rubber latex is a derivative of the *Hevea brasiliensis* (rubber) tree.[52] Healthcare providers and latex company workers are at risk of latex anaphylaxis so meticulous prevention of latex exposure is recommended. Accurate history-taking, identification of the specific IgE antibody, and the prick test may assist with diagnosis.[50,51] Furthermore, component-resolved diagnostics are valuable predictor tools.[20,53] Immediate allergic reactions to certain plant foods may occur in cases with latex allergy (known as latex fruit syndrome).[2]

Management

Anaphylactic shock is a life-threatening emergency that requires in-place emergency guidelines, equipment, medications (including preloaded adrenaline), and trained individuals in workplaces.[50,51]

CONCLUSION AND RECOMMENDATIONS

OAs are multidisciplinary diseases that impose a heavy burden on the healthcare system, economy, society, industries, and individuals worldwide. Close interaction and co-operation of allergists, occupational medicine specialists, immunologists, epidemiologists, social medicine specialists, internists, pulmonologists, and dermatologists, together with the support of social, industrial, and governmental authorities is mandatory to combat this group of conditions. Prevention and management of occupational allergies requires comprehensive guidelines for each of the diseases, and guidelines should be provided according to medical and occupational aspects. Furthermore, as occupational environments change over time, update classes should be scheduled at intervals. The guidelines must be easily available to workers and healthcare systems.

Employers are responsible for occupational hazards to their employees' health conditions, including allergic disorders, unless caused by the negligence of an employee. The employer should pay attention to their responsibilities, including prevention, cure, work cessation, compensation etc., if any occupational allergy threatens their employees. Additionally, insurance companies should be actively engaged in reduction of harm in the working environment for employees. They can help improve the implementation of preventive strategies and law execution in workplaces.

The establishment of a comprehensive occupational health surveillance system will provide valuable integrated information, which is useful for discovering new or known causative agents, detecting hazardous environments, and earlier

diagnosis. In general, the supportive and inspective role of legislation helps to decrease occupational injuries in the long-term. Particularly, the specific enforcement of regulations and laws to decrease environmental hazards will be more effective for employees, however it is not well-documented if penalties are useful.[54] General and specialised education of society, governors, workers, and managers should become mandatory, because it is the first step in improving attitudes, knowledge, and practice toward the goal of an allergy-free occupational environment. Finally, comprehensive attention to these recommendations will be beneficial to human health and to maintenance of financial resources. These strategies could subsequently reduce the economic burden to the healthcare system.

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ALLERGEN-SPECIFIC IMMUNOTHERAPY

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ABSTRACT

Allergen-specific immunotherapy remains the only causal treatment of allergic disease to date. Its efficacy in symptom reduction was demonstrated in double blind, placebo-controlled studies of allergic rhinoconjunctivitis, allergic asthma, and Hymenoptera venom hypersensitivity, including long-term effects after discontinuation of treatment. In addition, immunotherapy decreases the risk of developing new sensitisations to aeroallergens in monosensitised patients and allergic asthma in patients with mere allergic rhinitis. The mechanism of immunotherapy entails redirection of the T lymphocyte response from a T helper cell Type 2 phenotype in favour of induction of regulatory T cells and/or immune deviation toward a T helper cell Type 1 phenotype, with resulting inhibition of downstream effector pathways and induction of immunoglobulin G-associated blocking antibodies. Two main application forms are used in clinical practice: subcutaneous immunotherapy and sublingual immunotherapy. The advantage of subcutaneous immunotherapy is its proven efficacy over a broad range of indications. Disadvantages are systemic allergic reactions and inconvenience for the patient due to frequent doctor visits. Sublingual immunotherapy has been shown to result in less systemic allergic reactions and may be more convenient due to home application; however, efficacy has only been proven for allergic rhinitis. For clinicians, the adherence to practice guidelines and thorough knowledge of allergen products, application routes, indications, immunomodulatory mechanisms, efficacy, safety, and cost-effectiveness is important for successful treatment and will be addressed in this review article.

Keywords: Allergen-specific immunotherapy (AIT), immunomodulatory mechanism, cost-effectiveness, efficacy, safety, sublingual immunotherapy (SLIT), subcutaneous immunotherapy (SCIT).

INTRODUCTION

In Europe, allergen-specific immunotherapy (AIT) for hayfever was first introduced in 1911 by Noon and Freeman.[1,2] Treatment showed effectiveness and was frequently used in the 1920s and 30s for a range of seasonal and perennial allergens. Despite controlled clinical trials, which proved efficacy in respiratory disease[3] and in hypersensitivity to Hymenoptera venom,[4] a period of decreased use of AIT followed. This was firstly due to the introduction of safe and effective symptomatic treatments such as oral antihistamines and intranasal corticoid sprays in allergic rhinitis, and secondly to safety concerns.[5] The recent revival of AIT is due to increased safety with standardisation and modification of allergens, recognition of risk factors for systemic reactions (SRs), and the understanding of underlying immunomodulatory mechanisms and clinical benefits such as have been observed in the prevention of asthma development.[6,7] For successful treatment, adherence to practice guidelines[8,9] combined with the knowledge of allergen products, application routes, indications, immunomodulatory mechanisms, efficacy, and safety as well as management of allergic reactions is important.

ALLERGEN PRODUCTS

Allergens such as pollens, mites, and animal dander are preferable in a standardised form for regular administration and are subject to adequate quality control; their efficacy and safety should have been proven in controlled trials.[10] Available commercial allergen extracts for subcutaneous immunotherapy (SCIT) are either aqueous, depot, or modified extracts. Aqueous extracts are used for rush and cluster SCIT but have the disadvantage of increased

side effects.[10] In depot extracts the allergen is bound to a carrier to diminish degradation which reduces side effects and may increase efficacy. Modified extracts (recombinant allergens) contain a physical or chemical alteration. The intention is to increase safety through the reduction of allergenicity alongside the potential for immunomodulation. In Europe, mixing of unrelated allergens is not recommended, as efficacy has not been adequately investigated in clinical trials.[11] Cross-reacting allergens such as for grass species or different house dust mites may be administered as mixtures but have not been shown to have any advantage over single allergens due to substantial sequence of homology for shared major epitopes.[10]

APPLICATION ROUTES AND PRACTICAL MANAGEMENT

The decision on which route of immunotherapy to take depends, among other things, on assessment of relative contraindications and patient preference. Before starting treatment, the patient should receive written and verbal information about efficacy, adverse reactions, and application of treatment (duration and supervised observation times in clinic). Special emphasis should be made on the need for adherence to the treatment protocol, especially if treatment is self-administered at home.

The most common form of application is SCIT which involves repeated injections (preferably to the dorsal area of the upper arm). Depending on the extract, preseasonal courses (for seasonal aeroallergens) over a course of around 8 weeks with an ascending amount of allergen and for 3 years in a row, are available. Alternatively, an updosing phase with weekly injections over 2–3 months followed by a maintenance phase of 3 years can be applied. The 'cluster dose' regimen is an alternative in which the maintenance dose is achieved after shorter updosing (generally 7–8 weeks) with a similar safety profile. Finally, 'rush' and 'semirush' protocols are used in situations where fast tolerance needs to be achieved, as for example in patients with an allergy to Hymenoptera. The application of these protocols needs to be evaluated against an increased risk of SRs.[12]

The duration of AIT is usually 3 years for treatment with aeroallergens. For Hymenoptera immunotherapy for 5 years is often recommended, as evidence exists that 5 rather than 3 years may result in longer-lasting benefits.[13] Life-long treatment may even be considered for patients with life-threatening reactions: those with SRs during SCIT and those with honey bee allergy.[13]

Concerns about the practical management of SCIT exist largely due to patient inconvenience caused by the necessity of frequent medically supervised administration. These concerns have been addressed with the development of other application forms such as sublingual immunotherapy (SLIT). SLIT (both drops and tablets) is available for aeroallergens such as grass pollen, birch pollen, and house dust mite. The first dose is administered under supervision in the clinical setting followed by usually daily self-administration over the course of 3 years. Side effects are common, encompassing local symptoms such as itching and swelling of the mouth and throat which usually subsides within 2–6 weeks.[14] Grading is performed according to the severity of local symptoms and the need for symptomatic treatment or discontinuation of therapy. A small proportion of patients may have persistent symptoms but these are rarely so bothersome that treatment needs to be discontinued.[15] International consensus guidelines on AIT application exist[11] and before starting AIT the package insert and manufacturer product information about the AIT extract should be consulted.

INDICATIONS AND CONTRAINDICATIONS FOR ALLERGEN-SPECIFIC IMMUNOTHERAPY

The approach to treatment of allergic disease in general consists of the combination of allergen avoidance, medications for symptom relief, and education of the patient. Taking into account various different considerations, AIT may be indicated in respiratory disease, allergic rhinoconjunctivitis, allergic asthma, and in sensitivity to Hymenoptera venom (Table 1). Patients are treated from the age of 5 years and onwards.

Allergic Rhinoconjunctivitis

In allergic rhinoconjunctivitis, AIT is indicated in patients with bothersome moderate-to-severe symptoms despite guideline-directed pharmacotherapy (daily adherence to oral antihistamine and a nasal corticosteroid spray). This concerns about 20% of allergic rhinitis patients.[16] A clear history of the causative agent and supportive skin, as well as immunoglobulin (Ig)E tests are required before starting therapy.

Table 1: Considerations in different indications for allergen-specific immunotherapy.

Indication for allergen-specific immunotherapy	Considerations
Allergic rhinitis and allergic asthma	• Evidence of specific IgE antibodies to clinically relevant allergens • Patient preference • Adherence • Response to avoidance • Response to symptomatic medications • Adverse reactions to symptomatic medications • Coexistence of allergic rhinitis and asthma • Possible prevention of asthma in patients with rhinitis
Reactions to Hymenoptera stings	• History of a systemic reaction to a Hymenoptera sting (especially if associated with cardiovascular and respiratory symptoms and evidence of clinically relevant specific IgE antibodies) • Patients >16 years old with a history of cutaneous symptoms and clinically relevant specific IgE antibodies • Frequent and large disabling local reactions may potentially be an indication

IgE: immunoglobulin E.
Adapted from Cox et al. 2011[9]

In order to improve accuracy of diagnosis and precision of therapy, component-resolved diagnosis and the identification of minor and major allergens in a patient should be considered.[17] For example, in a patient with a minor allergen as the major sensitiser, one may decide against AIT as the commercial extracts are standardised only for major allergens, which may lead to lack of effectiveness of AIT in this patient and more seriously, may result in adverse events.[18] AIT should only be considered if markers of specific genuine sensitisation are positive and in accordance with clinical symptoms. Patients that profit most from treatment have been those who were unresponsive to available symptomatic treatment, had side effects to conventional treatment, and had complications of rhinitis (e.g. sinusitis). Treatment failure may occur in patients and this could be due to the poor quality of allergen extracts used in AIT.[19] Sensitisation to minor allergens is also a factor as it may not be available in commercial extracts.[18] Another reason for treatment failure is the lack of clinical relevance of those allergens applied. This is why previous detailed diagnostics are of eminent importance. Hymenoptera AIT is very effective, however a few fatalities have been reported in patients undergoing or following SCIT for Hymenoptera therapy after a field Hymenoptera sting. These usually include patients with other risk factors such as mastocytosis.[10]

Allergic Asthma

In allergic asthma, treatment is most effective in those patients who only recently started to perceive asthma symptoms. In patients with allergic asthma, AIT may reduce exacerbation rate[20] but care must be taken to ensure optimal asthma control before starting immunotherapy and during maintenance treatment. Patients with severe asthma, uncontrolled asthma, and frequent exacerbations are specifically excluded.

Venom Immunotherapy

Venom immunotherapy is indicated in patients with severe systemic allergic reactions and documented sensitisation. In cases where a milder reaction occurs other factors may have to be taken into account such as availability of healthcare, hobbies (e.g. bee keeping), and comorbidities (e.g. cardiovascular disease and mastocytosis). Large local reactions are not an indication for treatment. In guidelines for children with urticaria alone, immunotherapy is not recommended (risk of SR is 5%). Those patients who had SRs have a much higher risk of experiencing another SR (30–60%) in contrast to those with large local reactions only (5–10%).[21]

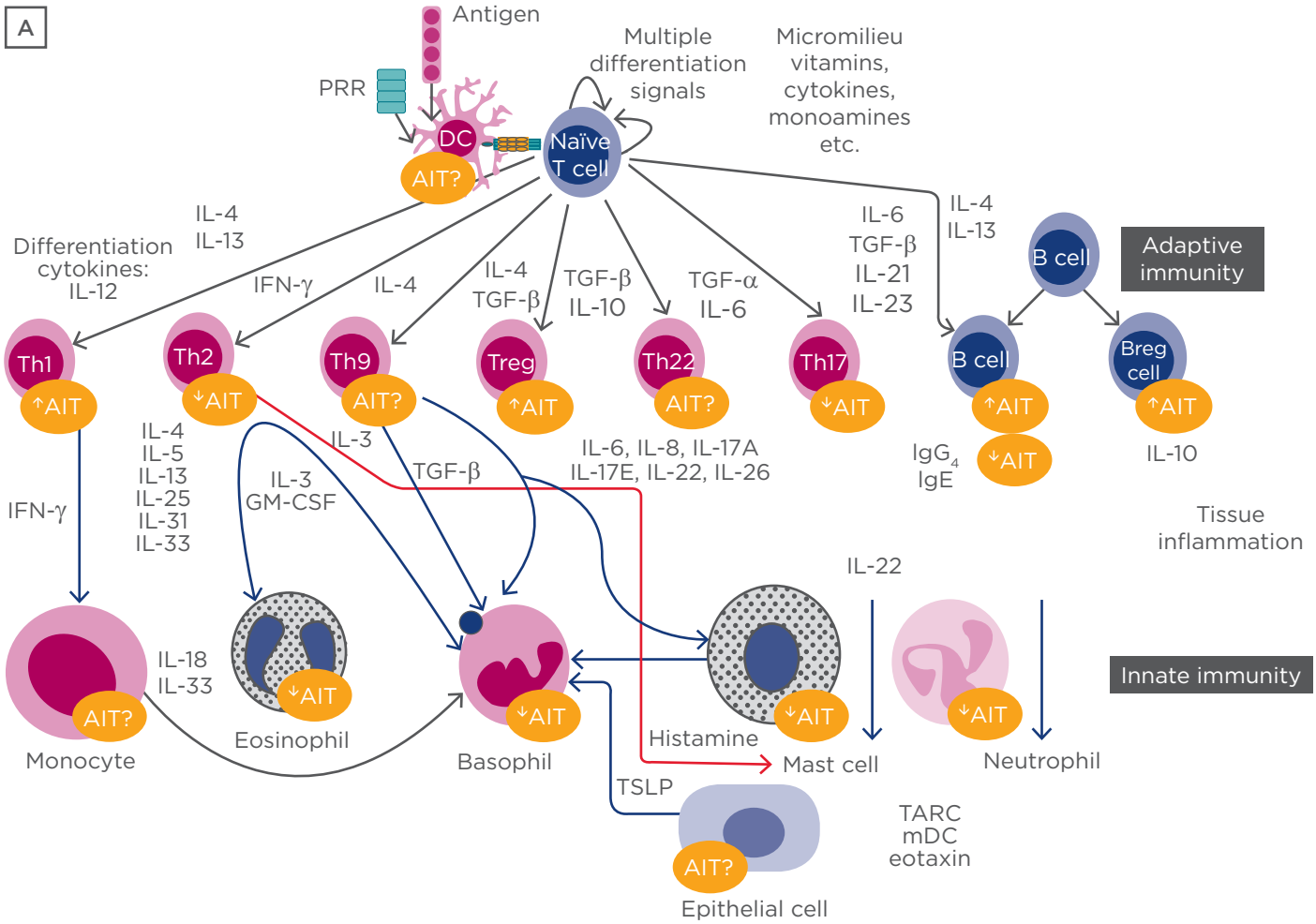
Contraindications for starting AIT are cardiovascular disease, severe uncontrolled asthma, treatment

with beta blockers (due to the risk of refractory anaphylaxis), compliance concerns, and pregnancy.[9,11] Risks and benefits need to be evaluated in these individuals. Uncontrolled asthma remains the most important risk factor for severe adverse events and therefore, effective asthma therapy may need to be established first in order to achieve control before considering AIT. Official guidelines do not provide clear recommendations for this condition.[22] In patients treated with beta-blockers the indication of this medication needs to be evaluated; if possible, together with the treating cardiologist or general practitioner. Therapy should be changed to another antihypertensive agent before starting AIT, athough temporary discontinuation of a short-acting beta blocker prior to injection may be an option. If the contraindication risks outweigh the benefits for AIT it should be applied with caution and only by trained personnel in a clinical setting equipped for severe anaphylaxis.[9,11] In cases of a beta blocker therapy, glucagon must be available for treatment of refractory anaphylaxis.[23,24] On the other hand, the continuation of AIT during pregnancy seems to be safe if treatment is started before pregnancy.[25] Finally risk-benefit needs to be evaluated in special cases; this includes individuals with venom allergy, cardiovascular disease, and beta blocker treatment which cannot be stopped. In these instances, AIT may still begin, but requires thorough monitoring.

MECHANISM

AIT reduces early and late phase responses to allergen challenge in target organs such as nose and lungs as well as to intradermal allergen challenge.[26] The immunmodulatory mechanism is complex[27] and several immunological effects have previously been described (Figure 1).[27]

When AIT is administered, a decrease in the susceptibility of mast cells and basophils is observed very early on in the process (for example, in AIT to Hymenoptera venom, a decrease is observed in the first 6 hours during the build-up phase). An upregulation of histamine Type 2 receptors with a suppression of FcεRI-induced activation of basophils has been proposed as a mechanism.[27,28]



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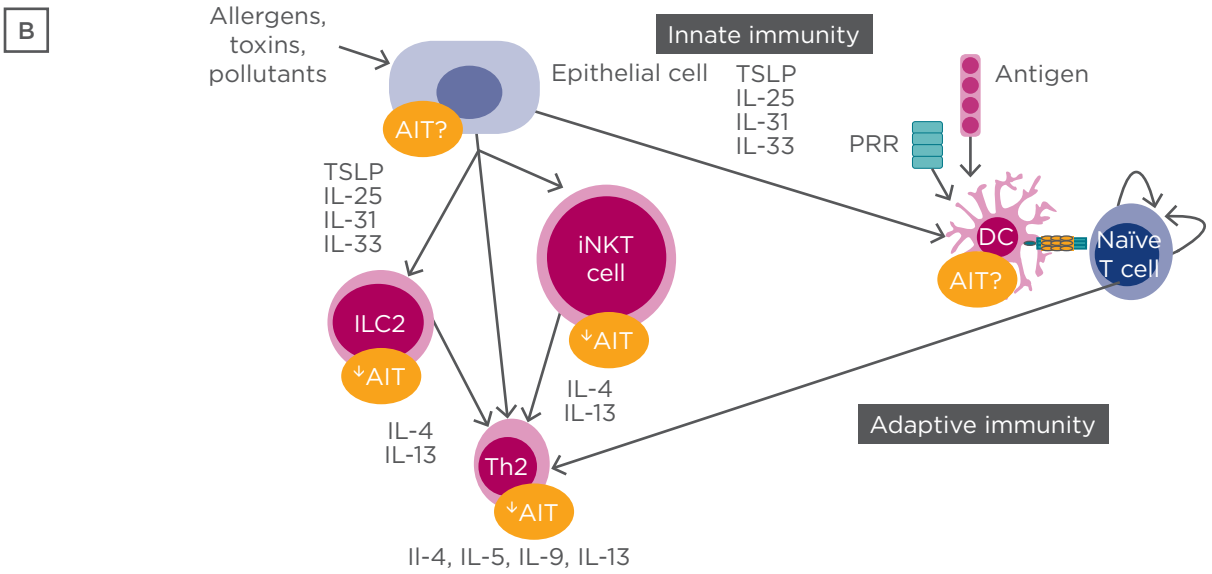

Figure 1: Cellular and molecular changes during AIT.[27]

A) Differentiation of naïve T cells after allergen presentation in the presence of innate immune response substances that trigger PRR and vitamins, monoamines that control cellular differentiation, and coexposed substances with the antigen and status of the cells and cytokines in the microenvironment is shown. Naïve T cells can differentiate into Th1, Th2, Th9, Th17, and Th22 cells. Based on their respective cytokine profiles, responses to chemokines, and interactions with other cells, these T cell subsets can contribute to general inflammation. The increase in Th1 and Treg cell numbers plays a role in counterbalancing other effector cells. The balance between allergen-specific effector T cells (particularly Th2 cells) and IL-10-producing Treg cells is decisive for the development or suppression of allergic inflammation. Treg cells and their cytokines suppress Th2 immune responses and contribute to the control of allergic diseases in several major ways. Similarly, induction of IL-10-producing Breg cells plays an essential role in suppression of IgE and induction of IgG_4.

B) The suppression of peripheral ILCs, especially ILC2s, may contribute to Th2 suppression and immunologic tolerance induced by AIT.

AIT: allergen-specific immunotherapy; Th: T helper; Treg: allergen-specific regulatory T cells; Breg: regulatory B cells; IL: interleukin; ILC: innate lymphoid cells; iNKT: invariant natural killer; TSLP: thymic stromal lymphopoietin; PRR: pattern recognition receptors; IFN-γ: interferon gamma; TARC: thymus and activation-regulated chemokine; mDC: macrophage-derived chemokine; DC: dendritic cell; GM-CSF: granulocyte-macrophage colony-stimulating factor; Ig: immunoglobulin; TGF: transforming growth factor.

In the process of building up immune tolerance over time, T cell and B cell tolerances are induced. A particular target of AIT is the suppression of Type 2 immune cells (T helper 2 [Th2] cells, Type 2 innate lymphoid cells, and Type 2 cytotoxic cells) which normally produce interleukin (IL)-4, IL-5, and IL-13 with an induction of inflammation by mast cell, basophil, and eosinophil activation (Figure 1B).[29,30] AIT generates, likely via involvement of dendritic cells and possibly other antigen-presenting cells, allergen-specific regulatory T (Treg) cells, while Th2 cells decrease[27] (Figure 1). Tregs, which are identified through high surface expression of CD4+CD25+, produce IL-10 which promotes IgG_4 switching and blocks IgE-facilitated antigen presentation by B cells[26,31] (Figure 1A). Inhibition of Th2 cytokines such as IL-4 inhibits Th2 cell development and B cell switching to IgE switching. Inhibition of IL-5 leads to downregulation of eosinophil activation and survival in tissues.[32] Production of tumour growth factor beta from Tregs is promoted, which induces B cell switching to IgA at mucosal surfaces.[10] A transient increase in specific IgE is observed early after start of therapy with blunting of seasonal increases.[26] As IgG_4 plays a key role in tolerance development further examinations of its affinity and specificity have taken place. It appears that during long-term administration the avidity and/or affinity of IgG_4 increases such that it becomes more efficient in competing with IgE for allergen binding, thereby blocking IgE-dependent functions such as basophil activation and IgE-facilitated antigen presentation.[33]

Table 2: Factors associated with adverse reactions or more severe adverse reactions to allergen-specific immunotherapy.[9,37,38,57]

- Uncontrolled asthma
- Dosage errors
- Induction phase of treatment
- Erroneous intravenous injection of dose
- Previous symptomatic reaction
- Extreme sensitivity to allergen
- Change to a vial of a new batch during maintenance therapy
- Pollen season
- Febrile illness
- Beta blocker
- Angiotensin-converting enzyme inhibitor (especially in venom allergy)

EFFICACY

AIT is effective in allergic rhinitis, allergic conjunctivitis, allergic asthma, and hypersensitivity to stinging insects.[9] It is likely that children will respond better than adults due to their shorter disease duration.[10] In contrast to symptomatic treatment, AIT has the potential to modify the pathophysiological mechanism of allergic disease leading to a sustained effect even after stopping treatment.[34]

SCIT has proven to be effective in treating allergic asthma, leading to an improvement in asthma symptoms and reduced medication. It has been estimated that it is necessary to treat three patients (95% confidence interval [CI]: 3–5) in order to avoid one's deterioration in asthma symptoms.[20] In seasonal allergic rhinitis, SCIT led to a significant reduction in symptoms (standardised mean difference [SMD]: -0.73; 95% CI: -0.97 to -0.5, p<0.00001) and medication score (SMD: 0.57; 95% CI: -0.82 to -0.33, p<0.00001).[16] In Hymenoptera allergy SCIT is the treatment of choice. Following SCIT, the rate of effective protection against a SR after a wasp sting is 95–98% and after a bee sting it is 80–85%.[13,21]

In a recent meta-analysis for SLIT a significant reduction in symptoms (SMD: -0.49; 95% CI: -0.64 to -0.34, p<0.00001) and medication requirements (SMD: -0.32; 95% CI: -0.43 to -0.21, p<0.00001) were seen in allergic rhinitis patients.[35] It has been shown to be efficacious and safe including induction of long-term remission for allergic rhinitis.[36] In allergic conjunctivitis SLIT induced a significant reduction in ocular symptoms (SMD: -0.41; 95% CI: -0.53 to -0.28).[37] According to a recent review, data for asthma outcomes in studies with SLIT is lacking, thus more research is necessary before a conclusion can be drawn in regards to efficacy and safety.[38]

Both SCIT and SLIT are effective therapies with evidence stronger in seasonal compared with perennial disease and stronger in adults compared with children.[39] Indirect comparison between the two treatments has been controversial.[39] Data on efficacy may favour SCIT whilst data on tolerability and safety favours SLIT. However, adequately powered, randomised, placebo-controlled, head-to-head trials are still needed.[39]

OTHER POSSIBLE INDICATIONS

A possible indication for AIT is atopic dermatitis in a patient sensitised to aeroallergens. In a recent meta-analysis authors found limited evidence that AIT may be an effective treatment for atopic dermatitis although further research is required.[40] Immunotherapy for food allergy has been studied but is not established in general clinical practice. Current meta-analyses indicate that oral immunotherapy for peanuts cannot be recommended for routine practice. Even though it may result in desensitisation, long-term tolerance appears unlikely and the risk of SRs substantial, at least with the currently available methods.[41] Similar results were found for oral immunotherapy in milk,[42] egg,[43] and fruit allergies.[44] AIT for latex has also been under investigation; both SCIT and SLIT treatment was effective overall even though SCIT was accompanied by the frequent occurence of side effects, while SLIT was better tolerated. Guidelines do not consider allergy to latex as an indication to desensitisation.[45]

SAFETY

The application of allergens to an IgE-sensitised patient inevitably carries the risk of an anaphylactic reaction. Adverse reactions to SCIT and SLIT are graded according to World Allergy Organization (WAO) guidelines.[14,46] According to safety recordings in the USA over the previous 50 years, one death per 2.5 million injections and one near-fatal reaction per 1 million injections occurs in SCIT.[20,47] In a recent report gathering data from 2008–2013, a total of four fatalities were reported in 28.9 million injection visits.[48] Additionally, 1.9% of patients experienced SRs (0.08% and

0.02% experienced Grade 3 and 4, respectively). The frequency of SR (any severity) was one in nine patients in a meta-analysis examining trials in patients with asthma.[20] SRs occurred in 1.4% of patients receiving SLIT tablets including 0.03% Grade 3, but without Grade 4 reactions or fatalities.[48] In Europe, since the famous report about several fatalities after SCIT in 1986,[5] fatalities have become rare and none have been reported in the last decade in Europe.[24] This is due to better knowledge and considerations of risk factors (Table 2) and improved adherence to practice parameter guidelines.[9]

Uncontrolled asthma remains a key risk factor for Grade 3 and higher SRs and lowering doses during the pollen season for highly positive skin tests reduced SRs in general ($p<0.05$).[48] Fatalities occured during the first hour after SCIT and in situations where adrenaline was not readily available. This emphasises the need for patient education and monitoring of asthma before injection, adequate post-injection time, supervision in a facility with trained staff, appropriate equipment for resuscitation, and readily available adrenaline for application.[48] Patients should be observed between 30 minutes (USA, most parts of Europe)[9] and 60 minutes (UK).

MANAGEMENT OF ADVERSE REACTIONS

Personnel should be trained to treat anaphylaxis and have appropriate treatment available. Most importantly, this includes adrenaline (1 mg/mL for injection; 0.3 mL intramuscularly is indicated in anaphylaxis), antihistamine (e.g. 1 x clemastin 2 mg/mL intravenously), corticosteroids (e.g. 1 x 250 mg methylprednisolone intravenously), inhaled bronchodilator (e.g. 1 x 100–200 µg salbutamol), intravenous supplies (e.g. normal saline for infusion as needed), and oxygen and suction equipment. The most important immediate intervention is adrenaline.

NOVEL APPROACHES

Novel treatments are currently under investigation in order to increase efficacy and reduce SRs of immunotherapy. Anti-IgE (omalizumab) has been used as an add-on therapy to increase both efficacy[49] and tolerability[50] with a dramatic reduction of SRs. Costs have to be considered and therefore omalizumab remains a treatment option only in selected cases. Another strategy to increase efficacy and safety of AIT is the use of an adjuvant. An example is bacterial immunostimulatory DNA sequences (such as immunostimulatory oligodeoxynucleotide sequences [ISS-ODN]) which are potent adjuvants to induce a strong Th1 response.[51] Allergen ISS-ODN in particular has shown encouraging results in inducing immunomodulation with reduced SRs in patients with ragweed sensitisation.[52] Furthermore, research has been performed in molecular vaccines including recombinant allergens, recombinant allergen derivates, and synthetic peptides in order to increase safety and efficacy of AIT with the aim of developing a preventive allergy vaccination.[53] In cat allergy for example, the use of short synthetic peptides which represent major T cell epitopes of the allergen have shown efficacy and tolerability with reduced ability to cross-link IgE as well as activate mast cells and basophils, thus avoiding IgE-mediated reactions.[54]

Finally, other routes of application apart from the well-established subcutaneous and sublingual route have received attention recently. One is the epicutaneous route, where an allergen is applied to the non-vascularised tissue. Clinical efficacy has been demonstrated in aeroallergy.[55] Furthermore, a reduction of food-induced anaphylaxis and an induction of Tregs has been demonstrated in mice.[56] Additionally, the intralympathic application of AIT may offer an interesting alternative. Efficacy and immunmodulation have been demonstrated in a study of 165 participants with only three injections in 8 weeks without SRs.[57] Intralymphatic immunotherapy is already being practiced in certain centres and a European Academy of Allergy and Clinical Immunology (EAACI) interest group has been established.

PHARMACOECONOMICAL CONSIDERATIONS

Insufficiently treated allergies cause a substantial direct and indirect economic impact ranging from €55–€151 billion per annum due to absenteeism and presenteeism.[58] Available treatment options are associated with different levels of cost-effectiveness and recommendations such as the Allergic Rhinitis and its Impact on Asthma (ARIA) guidelines have called clearly for the demonstration of cost-effectiveness of treatment.[8] A recent review comparing AIT with symptomatic treatment has shown evidence for cost savings from 6 years onwards for both SCIT and SLIT compared with standard symptomatic treatment

in respiratory disease.[59] Two main forms of economical evaluation have been performed in AIT. Cost-effectiveness studies addressed costs in monetary units and effects in physical units (e.g. symptom reduction), while cost-utility studies analysed the effect of treatment in health-related quality of life (e.g. quality-adjusted life years). Both cost-effectiveness and cost-utility studies[60-69] have been performed in SCIT and SLIT and most studies have confirmed cost-effectiveness for AIT in comparison with standard pharmacological treatment. AIT has the potential not only to decrease healthcare costs (doctor's visits and drug use) but also indirect costs including decreased loss of work days, especially in the long-term.[27] Unfortunately there is a lack of generalisability due to heterogeneity between studies.

CONCLUSIONS

AIT remains the only treatment that modifies the underlying causes of allergic disease with resulting long-term remission. The use of standardised allergens in which efficacy has been proven is recommended. Many products still lack adequate quality control and confirmation of efficacy, in particular allergen mixtures, which should be addressed in future research. The two main forms of application, SCIT and SLIT, have both been shown to have good efficacy and safety in allergic rhinitis. At present the choice between SCIT and SLIT depends largely on patient preference as adequate head-to-head trials are missing. Evidence in children for both application forms is weaker and should be further evaluated. SCIT is indicated in allergic asthma and Hymenoptera venom allergy. It may also be desirable to find alternative and possibly safer routes of applications for these indications. Further research needs to be performed in order to broaden the spectrum of indications to prevalent diseases such as atopic dermatitis and food and latex allergies. Finally, new treatment approaches are encouraging but need to be further evaluated in controlled clinical trials. More data on cost-effectiveness, especially in regards to long-term tolerance, remains an important goal.

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MANAGEMENT OF CARDIOVASCULAR RISK FACTORS IN TYPE 2 DIABETES MELLITUS PATIENTS

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ABSTRACT

People with Type 2 diabetes mellitus (T2DM), compared with non-diabetic individuals, have increased cardiovascular risk. Part of this excess risk is associated with a higher prevalence of other cardiovascular risk factors in these patients, such as obesity, dyslipidaemia, and hypertension. However, the increased cardiovascular risk present in T2DM cannot be attributed entirely to the high prevalence of traditional risk factors and other non-traditional risk factors may also be important for people with T2DM. Evidence suggests that in patients with T2DM, treatment of cardiovascular risk factors is very important in reducing the risk of cardiovascular disease (CVD). The poor control of risk factors observed in the diabetic population supports the need for more aggressive treatment of modifiable cardiovascular risk factors, especially in patients with previous CVD. There is little evidence on the independent association between traditional and non-traditional cardiovascular risk factors, however these risk factors do not appear in isolation and are produced at the same time, exacerbating the risk of a cardiovascular event. Targeting multiple markers of CVD risk offers the best chance of improving CVD outcomes. The objective of this review is to highlight the importance of managing cardiovascular risk factors in patients with T2DM.

Keywords: Type 2 diabetes mellitus (T2DM), cardiovascular disease (CVD), cardiovascular risk factors, dyslipidaemia, hypertension, obesity, microalbuminuria, homocysteine, subclinical cardiovascular disease.

INTRODUCTION

Individuals with Type 2 diabetes mellitus (T2DM), compared with non-diabetics have increased cardiovascular morbidity and mortality.[1] Diabetic vascular disease is associated with a 2–4-fold increase in the incidence of coronary heart disease and stroke, and 2–8 times the risk of heart failure.[2] The risk of cardiovascular disease (CVD) follows a gradient and the capture of this gradient depends on the combination of several risk factors.[3] Part of this excess risk is associated with a higher prevalence of risk factors in these patients, such as obesity, dyslipidaemia, and hypertension. Evidence suggests that in patients with T2DM, treatment of cardiovascular risk factors is very important in reducing the risk of CVD.[4,5] The poor control of most of the cardiovascular risk factors observed in the diabetic population[6] supports the need for more aggressive treatment of modifiable cardiovascular risk factors, especially in patients with previous CVD. However, the increased cardiovascular risk present in T2DM cannot be attributed entirely to the high prevalence of traditional risk factors and other non-traditional risk factors may also be important for people with T2DM.[7] Few studies have prospectively demonstrated in T2DM the independent association of non-traditional risk factors with traditional risk factors.[8] In addition, drugs that are currently used in the treatment of T2DM, such as insulin sensitisers and statins, have a variety of different effects on many of these non-traditional risk factors[9,10] which have been discussed extensively in the literature.[11] These risk factors do not appear in isolation but are produced at the same time,[12] exacerbating the risk of a cardiovascular event (Figure 1).

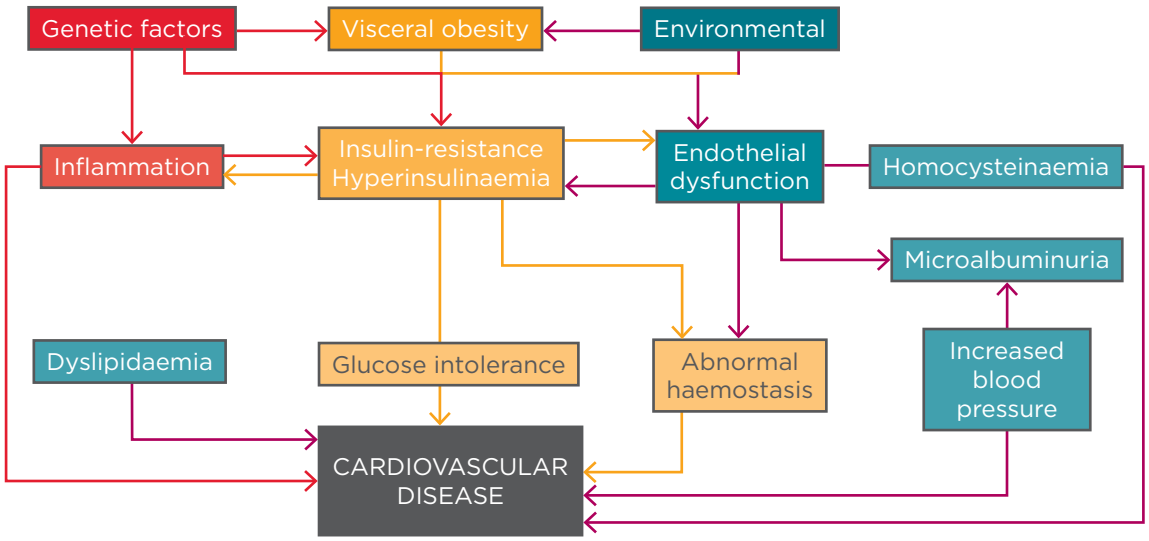

Figure 1: Interactions between traditional and non-traditional risk factors in the onset of cardiovascular disease in Type 2 diabetes mellitus patients.

Table 1: How cardiovascular risk factors affect cardiovascular complications in diabetes.

RISK FACTOR	MECHANISMS
Obesity	• Insulin resistance and defects in insulin secretion • Production of proinflammatory cytokines that causes an inflammatory state contributing to the development of atherosclerotic lesions
Alcohol	• Rise in blood pressure and heart rate without other favourable heart benefits
Hypertension	• Hyperinsulinaemia linked to increased renal reabsorption of sodium, increased sympathetic tone, and increased renin-angiotensin-aldosterone system activity
Cholesterol and lipoproteins	• Atherogenic lipid profile characterised by high triglycerides, low high-density lipoprotein cholesterol, increased apolipoprotein B synthesis, and small dense low-density lipoprotein particles
Smoke	• Elevates circulating free fatty acid levels • Impairs insulin sensitivity, directly or indirectly
Hypoglycaemia	• Rise in heart rate, systolic blood pressure, myocardial contractility, and cardiac output • Exacerbates ischaemia in individuals with occlusive coronary artery disease • Prolongs the QT interval • Deleterious effects on endothelial function, platelet reactivity, and coagulation • Increases inflammatory mediators and blood viscosity
Hyperhomocysteinaemia	• Atherosclerotic role
Microalbuminuria	• Systemic endothelial dysfunction • Glomerular endothelial dysfunction • Damage to glycocalyx, a protein-rich surface layer on the endothelium

The objective of this review is to highlight the importance of managing cardiovascular risk factors in patients with T2DM.

MECHANISMS OF INCREASED RISK

The abnormal metabolic state of diabetes accelerates atherosclerotic disease.[13] A variety of mechanisms can contribute to the increase in coronary heart disease, in addition to the effects on lipid metabolism and blood pressure (BP), with hyperglycaemia as the common trigger (Table 1). It is agreed that there is an increased prevalence of coronary plaques in diabetic hearts, with increased macrophage infiltration, a greater amount of lipid-rich atheroma, a higher incidence of thrombosis, and propensity for rupture.[14]

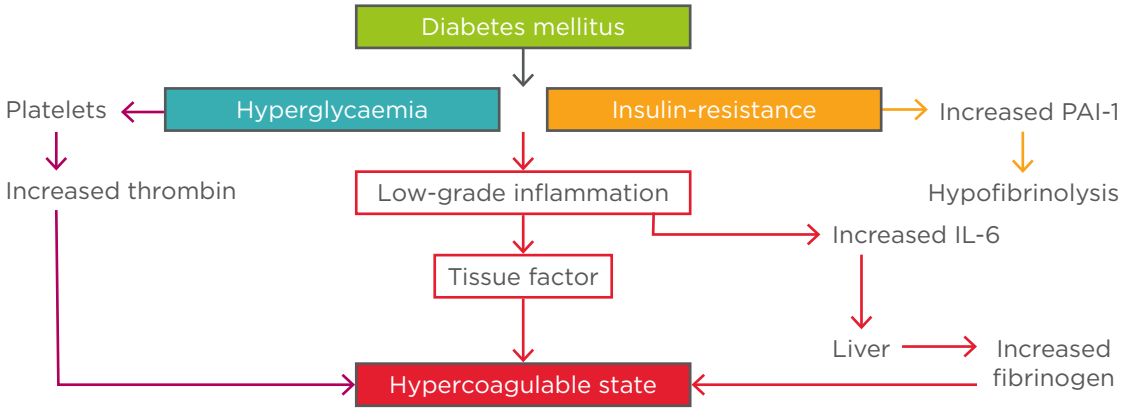

Figure 2: Prothrombotic mechanisms in diabetes mellitus.
IL: interleukin; PAI-1: plasminogen activator inhibitor-1.

The endothelium regulates vascular tone and the interaction of the vessel wall with blood cells and circulating substances.[15] Several mechanisms and biochemical changes cause endothelial dysfunction, including altered glucose metabolism, low grade inflammatory state, impaired insulin signalling, and increased reactive oxidant species generation. The duration of diabetes is related to the degree of impairment.[14] Insulin resistance, in particular, is significantly related to oxidative stress and endothelial dysfunction presents in its early stages. Moreover, hyperglycaemia generates advanced glycation end products that interfere with endothelial cell function and inhibit nitric oxide biosynthesis.[15,16]

Diabetes predisposes patients to abnormalities in pathways involved in coagulation, fibrinolysis, and haemostasis, which increase the risk of thrombus formation (Figure 2). T2DM patients have elevated coagulation factors and impaired fibrinolysis; fibrinogen plasma levels are increased and it is associated with progression of coronary artery calcification. On the other hand, fibrinolytic activity is reduced because circulating tissue-type plasminogen activator activity is decreased as a result of elevated levels of plasminogen activator inhibitor-1; these levels are higher in patients with poorly controlled T2DM.[14,17]

Platelets of diabetic patients have a hyper-reactive phenotype with enhanced adhesion, activation, aggregation, and alpha-granule content release that contribute to accelerated atherosclerosis. The higher adhesion is mediated principally by an increased expression of adhesion molecules and receptors located in the platelet surface, in particular glycoprotein IIb/IIIa and glycoprotein Ib, respectively, which mediate binding to platelet-fibrin and von Willebrand factor interaction. Hyperglycaemia and insulin deficiency and resistance contribute to platelet aggregation and activation by different pathways.[14,18]

TRADITIONAL RISK FACTORS

Obesity

Obesity has been linked to insulin resistance and defects in insulin secretion. Obesity also leads to the production of proinflammatory cytokines that cause an inflammatory state, contributing to the development of atherosclerotic lesions.[19] The primary approach to weight management is a change of lifestyle. A study showed that in the first few years an intensive lifestyle intervention with caloric restriction and increased physical activity produced a weight loss higher than standard intervention with improvements in BP, blood glucose, and lipid profile.[20] When the study was prolonged, it did not find a difference in the rate of cardiovascular events when compared with a standard nutritional intervention.[20] Lifestyle changes can produce a 3–5% rate of weight loss safely. These reductions can be maintained over time and the necessity for medication to control CVD risk factors is reduced.[21]

Different dietary patterns such as the Mediterranean diet, vegetarian, or vegan dietary approaches can be implemented to stop hypertension; low fat and low carbohydrate diets are effective for improving glycaemia and CVD risk factors.[21,22]

In T2DM patients, aerobic and resistance exercise produce noticeable benefits and their effects

are higher in combination compared with each being performed in isolation. Aerobic exercise is recommended for ≥150 minutes per week, ≥3 days per week, and preferably should be increased to 5 days with no more than 2 consecutive days between periods of activity at 40–60% of maximum aerobic capacity. Resistance exercises should be practised 2–3 times per week on non-consecutive days with a moderate intensity including 5–10 exercises during each session with 10–15 repetitions of each exercise.[23]

Bariatric surgery is the most effective treatment for weight loss and improves comorbidities for patients with morbid obesity or a BMI ≥35 kg/m^2 who have multiple conditions and do not respond to standard treatment. These changes have been observed before a significant weight loss, and seem to be consequences of gastrointestinal anatomy restructuring and neuroendocrine mechanisms.[21]

Alcohol

The consumption of a moderate amount of alcohol confers cardiovascular protection[24] and has been associated with a decreased incidence of heart disease in patients with DM and a decreased incidence of DM within a healthy population;[21,25] it is even advised by some associations.[26] However, a meta-analysis of 38 observational studies suggests that previous works overestimate the risk reductions[27] and others show different conclusions, such as a rise in BP and heart rate without other favourable heart effects, or that chronic alcohol consumption, even when it is low or moderate, may trigger the progression or development of T2DM.[28,29]

Hypertension

Hypertensive diabetic patients are at increased risk of morbidity and cardiovascular mortality. In these patients, elevated BP often occurs before the onset of a moderate increase in albuminuria. In the pathophysiology of hypertension in diabetics the development of diabetic nephropathy is involved, there is expansion of extracellular fluid volume, and increased arterial stiffness.[30] Hypertension is related to hyperinsulinaemia linked to increased renal reabsorption of sodium, increased sympathetic tone, and increased renin-angiotensin-aldosterone system activity.[31]

It is important to control BP levels at an early stage.[32] According to the recommendations of the American Diabetes Association (ADA) 2016,[33] patients with BP >120/80 mmHg should be advised on lifestyle changes such as weight loss, reduced fat diet, exercise, salt restriction, and not smoking or drinking alcohol excessively. Patients with BP ≥140/90 mmHg should start antihypertensive medications. The target BP for most people with DM is <140/90 mmHg. Achieving a lower systolic BP (e.g. <130 mmHg) may be appropriate for younger patients who do not require multiple drugs to achieve it.[34,35] In people aged 40–70 years, for every 20 mmHg increase in systolic BP or 10 mmHg increase in diastolic BP, CVD risk doubles (BP values ranging from 115/75–185/115 mmHg).[30] In clinical trials, antihypertensive therapy has been associated with a 35–40% reduction in the incidence of stroke, a reduction of 20–25% in the incidence of myocardial infarction, and a reduction of >50% in heart failure.[36]

Antihypertensive drugs of choice in diabetics are angiotensin-converting enzyme (ACE) inhibitors and angiotensin II receptor blockers. These drugs have no substantial toxicity or side effects, except for cough and raising the plasma potassium concentration in patients with underlying hyperkalaemia or renal insufficiency. Also, they may lower the plasma glucose concentration by increasing responsiveness to insulin[37] and have no effect on lipid metabolism. They protect against the progression of moderately increased albuminuria and severely increased albuminuria due to T1 and T2DM and have been evaluated for primary prevention of diabetic nephropathy.[38,39] They may also slow the progression of retinopathy.[40]

Angiotensin II receptor blockers seem to have the same benefits as ACE inhibitors in terms of renal protection in patients with nephropathy due to T2DM.[38,39] The LIFE trial in which the efficacy of these drugs was compared with a beta blocker reported a significant reduction in cardiovascular morbidity and mortality with losartan in a subset of high-risk patients.[41] The combination therapy of an ACE inhibitor and angiotensin II receptor blocker is not recommended as it has been observed that most benefits are not achieved and side effects increase compared with monotherapy.[42]

Thiazide diuretics at low doses (for example 12.5mg or 25mg per day of hydrochlorothiazide) are a good antihypertensive treatment for diabetics, especially in combination with ACE inhibitors and angiotensin II receptor blockers. The combination reduces diuretic-induced hypokalaemia, hyperlipidaemia, and hyperuricaemia.[43] Beta

blockers are an effective treatment for hypertension in diabetic patients, but are not recommended due to the modest worsening of glycaemic control seen with metoprolol and other beta blockers that also has been associated in non-diabetic patients with a higher incidence of new-onset diabetes.[44] Calcium channel blockers are a treatment option for hypertension in diabetics in combination therapy with ACE inhibitors or angiotensin II receptor blockers.[42] Alpha blockers are not a first-line therapy for hypertension in these patients due to their adverse effects, such as orthostatic hypotension, but would be an option for combination therapy in older male patients with prostatism.

Cholesterol and Lipoproteins

In T2DM, dyslipidaemia is characterised by a atherogenic lipid profile with high triglycerides, low high-density lipoprotein cholesterol (HDL-C), increased apolipoprotein B synthesis, and small dense low-density lipoprotein (LDL) particles.[45] This LDL subtype plays an important role in atherogenesis. Clinical trials widely demonstrate that lowering LDL-C with drugs reduces the risk of major coronary events regardless of diabetes status.[46]

Recommendations for lipid management in Type 2 diabetes mellitus

T2DM patients must reduce their intake of cholesterol, saturated, and trans-fat, and increase omega-3 fatty acids, viscous fibre, stanols/sterols intake, weight loss, and physical activity.

Low-density lipoprotein cholesterol

Elevated LDL-C is identified as the primary target of lipid-lowering therapy by both the American Heart Association (AHA) and the ADA. The new American College of Cardiology (ACC)/AHA cholesterol guidelines indicate that all patients with DM between the age of 40–75 years and with LDL-C levels between 70–189 mg/dL should be treated with a moderate-intensity statin (ACC/AHA Class I; ADA Level of Evidence A). Patients with DM between 40–75 years of age and with a ≥7.5% estimated risk of CVD, should be treated with statin therapy of high intensity (ACC/AHA Class IIa; ADA Level of Evidence B). Among individuals with DM who are <40 or >75 years of age, practitioners should evaluate the benefit of statin treatment (ACC/AHA Class IIa; ADA Level of Evidence C).[47] Since 2015, the ADA practice guidelines are concordant with the AHA guidelines.[33]

Triglycerides

Triglyceride-rich lipoproteins represent a secondary target of lipid-lowering therapy. The 2013 ACC/AHA guidelines on the treatment of cholesterol provide no evidence-based recommendations for the evaluation or treatment of hypertriglyceridaemia to reduce CVD risk.[47] In accordance with the National Cholesterol Education Program Adult Treatment Panel III (NCEP ATP III) Guidelines, the panel continue to recommend the evaluation of secondary causes and the treatment of patients with fasting triglycerides >500 mg/dL to prevent more severe hypertriglyceridaemia and pancreatitis. ADA clinical practice guidelines 2016 indicate that combination therapy (statin/fibrate and statin/niacin) has not been shown to provide additional cardiovascular benefit above statin therapy alone and is not generally recommended.[33] However, therapy with statin and fenofibrate may be considered for men with both triglyceride level ≥204 mg/dL (2.3 mmol/L) and HDL-C level ≤34 mg/dL (0.9 mmol/L).[33]

High-density lipoprotein cholesterol

HDL-C is not a target for therapy according to the ACC/AHA cholesterol treatment guidelines.[47] However, the ADA recognise desirable levels of HDL-C are >40 mg/dL in men and >50 mg/dL in women.[33]

Sex

It is known that some of the most common acute coronary syndromes in women are myocardial infarction associated with non-obstructive coronary artery, spontaneous dissection of the coronary artery, and stress-induced cardiomyopathy syndrome (Takotsubo syndrome). Women are also more likely to present with heart failure with preserved ejection fraction, and peripheral arterial disease.[48]

Smoke

Smoking acutely elevates circulating free fatty acid levels,[49] a negative factor for insulin-mediated glucose uptake. It is possible that nicotine impairs insulin sensitivity via this mechanism, directly or indirectly. The Framingham Study[50] showed that smokers have an increased risk of myocardial infarction or sudden death. In addition, there was a relationship between risk and the number of

cigarettes smoked per day, while former smokers had a morbidity and mortality from coronary heart disease similar to that of individuals who had never smoked.[50]

NON-TRADITIONAL RISK FACTORS

Hypoglycaemia

Hypoglycaemia is a well-recognised side effect of glucose lowering therapies and a major factor limiting glucose control in diabetic patients, particularly in those with long-standing disease.[51] There are several mechanisms by which hypoglycaemia may promote adverse cardiovascular outcomes.[52-54] Contra-regulatory hormones release and autonomic neural activation occurs when glucose falls below 70 mg/dL; these changes include a rise in heart rate, systolic BP, myocardial contractility, and cardiac output. These effects may exacerbate ischaemia in individuals with occlusive coronary artery disease. Hypoglycaemia also prolongs the QT interval and has deleterious effects on endothelial function, platelet reactivity, and coagulation, and increases inflammatory mediators and blood viscosity. Patients treated with insulin or insulin secretagogues should be asked regularly about the occurrence of hypoglycaemia, and therapy should be adjusted.

Hyperhomocysteinaemia

The close relationship between hyperhomocysteinaemia and CVD confirms the atherosclerotic role in the same.[55] Homocysteine may be elevated in blood enzyme genetic defects, nutritional deficits of vitamin cofactors, renal failure, smoking, etc. Hyperhomocysteinaemia is an independent cardiovascular risk factor. To reduce the concentration of homocysteine it is necessary to treat patients with folic acid, vitamin B6, and vitamin B12. In one study the levels normalised within 2–6 weeks.[56]

Microalbuminuria

The epidemiology of microalbuminuria reveals a close association with systemic and glomerular endothelial dysfunction and in particular, damage to glycocalyx, a protein-rich surface layer on the endothelium.[57] Microalbuminuria is a marker for diabetic nephropathy and an early marker of vascular damage.[58] Determination of microalbuminuria has been shown to be useful to identify patients with T2DM at a high risk of renal disease and CVD development.[59] Microalbuminuria is associated with higher cardiovascular mortality, especially in diabetics, but the direct association between microalbuminuria and vascular wall properties is still not clear.[60] The treatment of choice is antihypertensive angiotensin inhibitors, although administration of aspirin and a statin should be considered for diabetic patients.

ASPIRIN THERAPY

Currently the potential to use aspirin for the primary prevention of CVD events in diabetic patients remains controversial. In secondary prevention, aspirin reduces CVD events[61] and in the general population, aspirin is effective in preventing non-fatal myocardial infarction in men; for women, the evidence is less clear but aspirin appears to reduce the risk of stroke.[62]

Current Clinical Guidelines for Aspirin Administration in Primary Prevention Recommendations[33,63]

Low-dose aspirin (75–162 mg/day) is recommended for patients with a 10-year CVD risk of ≥10% and without an increased risk of bleeding (ACC/AHA Class IIa; Level of Evidence B) (ADA Level of Evidence C). This includes most men or women with diabetes aged ≥50 years who have at least one additional major risk factor (family history of premature atherosclerotic CVD, hypertension, smoking, dyslipidaemia, or albuminuria). Low-dose aspirin is reasonable in adults with DM at intermediate risk (10-year CVD risk, 5–10%) (ACC/AHA Class IIb; Level of Evidence C) (ADA Level of Evidence E). Aspirin should not be recommended for atherosclerotic CVD prevention for adults with diabetes at low atherosclerotic CVD risk (10-year atherosclerotic CVD risk <5%), such as in men or women with diabetes aged <50 years with no major additional atherosclerotic CVD risk factors, as the potential adverse effects from bleeding likely offset the potential benefits. (ADA Level of Evidence C).

SUBCLINICAL CARDIOVASCULAR DISEASE ASSESSMENT

It has been difficult to demonstrate that detecting CVD in its preclinical or subclinical state will reduce event incidence or enhance overall patient outcomes, especially in an era when aggressive CVD risk factor reductions are widely endorsed for this population.[21]

Screening Tests for Asymptomatic Cardiovascular Disease in Diabetic Patients

Electrocardiogram

Electrocardiograms (ECGs) may detect evidence of prior myocardial injury or ischaemia. In cohort studies, pathological Q waves, left ventricular hypertrophy (particularly if accompanied by repolarisation abnormalities), QRS prolongation, ST-segment depressions, and pathological T-wave inversions are associated with increased risk of CVD events. Data from the UK Prospective Diabetes Study (UKPDS) demonstrate that an abnormal ECG is an independent risk factor for all-cause mortality and fatal myocardial infarction in diabetic patients. Nowadays, ECG is not recommended by the ADA, however the AHA says that it is reasonable to obtain a resting ECG in asymptomatic adults with diabetes.[64-66]

Other screening tests

Other screening tests are exercise or pharmacological myocardial perfusion imaging (nuclear scintigraphy), exercise or pharmacological stress echocardiography, ankle-brachial index, and coronary artery calcium scoring by electron-beam computed tomography.[21] Nowadays further large and randomised trials are needed to determine whether screening for subclinical CVD can reduce CVD event rates in diabetic patients.[21]

CONCLUSIONS AND FUTURE DIRECTIONS

There is consistent evidence that optimal glycaemic control, along with control of cardiovascular risk factors, is necessary for reducing CVD in T2DM patients. Targeting multiple markers of CVD risk hopefully offers the best chance of improving CVD outcomes. There have been advances in our understanding of the role of non-traditional risk factors for CVD in T2DM. This understanding should gradually lead to development of more effective therapeutic strategies to prevent cardiovascular events. Research efforts need to focus on the factors that make islets susceptible to dysfunction and failure, particularly those that are acquired in early life, as these may be preventable. Epigenetic regulation of metabolic genes may be one of these fields.

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ROLE OF COAGULATION FACTOR CONCENTRATES IN THE OPERATING ROOM

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ABSTRACT

The use of fresh frozen plasma, cryoprecipitate, and platelets has been the mainstay of approaches to correct coagulopathies that can arise in the perioperative setting. Limitations include the time delay from obtaining results of coagulation screens to the availability of thawed fresh frozen plasma and the potential of fluid overload. With advances in both global haemostatic testing and concentrates of coagulation factors, there are increasing opportunities for innovative practice. However, there remains a paucity of studies that can provide good quality, unbiased evidence. These issues are elaborated here to form the basis for future study.

Keywords: Fibrinogen concentrate, fresh frozen plasma (FFP), prothrombin complex concentrate (PCC), coagulation monitoring, surgery.

INTRODUCTION

Haemostasis is a natural defence against vascular injury and haemorrhage. In the context of elective surgery, the challenge of maintaining adequate haemostasis is directly proportional to the nature and duration of the operation. The initiation trigger is via tissue factor exposure from subendothelial sites to cause factor VII activation, which then leads to amplification and propagation of the coagulation process (Figure 1).[1] These pathways are well described elsewhere and the key enzymatic stages share the common template of requiring a vitamin K-dependent protein (e.g. factors VII, X, or II) and a cofactor (e.g. tissue factor, factors VIIIa or Va) assembling on phospholipid surfaces in the presence of calcium.[2] Such reactions, which are referred to as tenase or prothrombinase, respectively, accelerate coagulation activation by several 100,000-fold to ensure explosive thrombin generation.[3]

Thrombin is the cascade enzyme as it is not only essential for procoagulant consequences, through the conversion of fibrinogen into fibrin and the activation of platelets, but also in activating the protein C anti-coagulant pathway.[4] This is particularly important at the margins of injury through thrombomodulin cofactor function to contain the extent of clot formation.[4] The cross-linking of fibrin is the ultimate step in the coagulation cascade, with clot stabilisation by thrombin-activated factor XIII. The action of thrombin-activatable fibrinolysis inhibitor (TAFI) also serves to reduce the rate of clot breakdown as part of thrombin-induced tissue-type plasminogen activator (tPA) profibrinolytic actions.[5]

From a physiological perspective, this would suggest a well-regulated homeostatic process involving equal and opposite reactions resulting from thrombin generation *in vivo*. As long as the surgical or traumatic insult is not excessive, exogenous haemostatic support is unlikely to be necessary peri or postoperatively. However, in the event of unplanned surgery in the presence of infection, such as in peritonitis or for major trauma, the haemostatic capacity may be compromised. This is true even in young patients with no medical history who develop significant coagulopathy perioperatively after major trauma.[6] The resulting coagulopathy in such circumstances presents a major challenge for anaesthetists and intensivists as it is typically multifactorial and the clinical

status can deteriorate rapidly. It is thus important to address this problem with prompt and comprehensive clinical assessments of coagulopathy followed by appropriate and timely administration of haemostatic therapy. This review discusses the current issues around plasma transfusion support, current concepts in coagulation monitoring, and understanding the roles played by non-activated coagulation factor concentrates as perioperativetherapy for achieving haemostasis. Activated prothrombin complex concentrates (PCCs) are not reviewed here as they are typically considered in the acquired haemophilia setting. Anti-coagulant factor concentrates have certain indications in the operating room setting but are beyond the scope of this manuscript.

CURRENT ISSUES IN PLASMA TRANSFUSION SUPPORT

Primary haemostasis upon vascular injury is mediated by platelets and reinforced by coagulation factors. Transfusion of plasma and platelets has been the mainstay of haemostatic therapy for many decades. Therefore, delayed decision or administration of blood products after prolonged storage can exacerbate coagulopathy and potentially affect clinical outcomes,[7] primarily due to the risk of exsanguination, and secondarily because clot formation is a defence mechanism against infection. Equally, premature and overzealous use of blood products can be harmful. For example, studies in intensive care patients have shown an increased risk of arterial thrombosis and death with platelet transfusions in the presence of consumptive thrombocytopenia.[8] This underscores the importance of timeliness in decision making and action.

Commonly used laboratory haemostasis assessment includes prothrombin time (PT), activated partial thromboplastin time (aPTT), fibrinogen level by the Clauss method, and platelet count. Typical turnaround time for these tests is in the region of 30–90 minutes which is not optimal in diagnosing coagulopathy or guiding haemostatic interventions. This is particularly problematic when multiple units of fresh frozen plasma (FFP) must be thawed according to laboratory procedure, which adds 30–60 minutes of processing time.

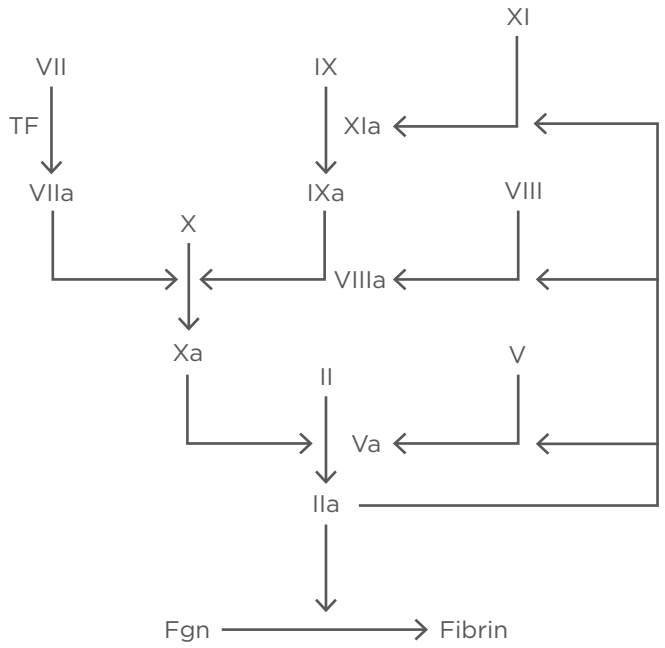

Figure 1: Schematic representation of how coagulation factor replacement promotes haemostasis.
Initiation of coagulation activation via the TF pathway leads to tenase and prothrombinase reactions to generate thrombin (IIa). This can then amplify the process through thrombin-mediated generation of factors IXa, VIIa, and Va. Thrombin conversion of Fgn to fibrin is then propagated. Fresh frozen plasma contains all of these coagulation factors in an unactivated form, whereas available coagulation factor concentrates provide those that are vitamin K-dependent; i.e. factors II, VII, IX, and X, with VII being the most variable between products.
TF: tissue factor; Fgn: fibrinogen.

FFP can contain variable but near normal levels of pro and anti-coagulant proteins and coagulation inhibitors. The relatively low concentrations of coagulation factors in therapeutic FFP (as compared to concentrates) makes it difficult to achieve a significant increase in patients' circulating levels without administering large volumes. Based on rough guidance, as much as 2.5 L of plasma transfusion may be required to improve clot times.[9,10] On the other hand, coagulation factor concentrates enable larger increases without large infusion volumes.[11] Large volumes of plasma transfusion are poorly tolerated in patients with limited cardiopulmonary reserve and can lead to intractable fluid overload. In addition, transfusion-related acute lung injury (TRALI) is a potentially lethal complication of plasma transfusion, although the preferential use of male donor plasma has significantly reduced its incidence.[10,12]

Although FFP has been available for approximately 60 years, evidence from randomised controlled trials (RCTs) proving its efficacy and safety is lacking, and recommendations in current guidelines (Table 1) are mainly based on observational studies.[13-15] In addition, studies from Europe, Canada, USA, and Australia have shown that both the use of FFP and cryoprecipitate are often inappropriate for reasons outside of clinical guidelines.[13,14] Administering FFP in patients with minimally elevated international normalised ratio values has been shown to be ineffective in producing meaningful corrections.[9,16]

RATIONALE FOR USING COAGULATION FACTOR CONCENTRATES

Prothrombin Complex Concentrates

In view of the practical problems of administering FFP, PCC could be advantageous because of the smaller volume required to replace deficient factors and the relative speed in reconstituting a lyophilised powder with 10–20 mL of sterile water. However, PCC only contains vitamin K-dependent proteins, i.e. factors II, VII, IX, and X, and acquired deficiency of factors V and VIII would not be remedied. Different formulations contain varying amounts of proteins C and S but PCCs are mainly distinguished by their factor VII content.[17] These are often referred to as three or four factor concentrates based on the levels of factor VII. PCC is licensed primarily for the management of bleeding in patients treated with vitamin K antagonists (VKA).[15,18] In Europe, there is a broad indication for PCC in the management of patients with low levels of factors II, VII, IX, and X. In the perioperative setting, PCC is often used in the management of severe bleeding in patients undergoing cardiovascular or other surgeries,[19,20] especially those with prolonged PT.[15] An advantage to their use is the reduced likelihood of TRALI due to the lack of antibodies in PCC. As to whether these products can induce further activation of coagulation and lead to adverse clinical outcomes, a meta-analysis of 27 studies for the reversal of VKA showed the overall incidence of thromboembolic complications as 1.4%.[21] The authors concluded that there was a 'low but quantifiable' risk of thromboembolic events in patients receiving PCC, but there was no direct comparison against a control (non-PCC treated group). The mortality rate was 10.6% and only a few cases could be attributed to thromboembolic events. As such, a clear link between PCC use and mortality from thromboembolic complications could not be made.[21] Data from PCC infusion in a porcine model of liver injury indicate that a dose of 50 IU/kg precipitated thromboembolism in all tested animals with disseminated intravascular coagulation observed in 44% of cases.[22] These findings raise the prospect that high PCC concentrations might cause adverse clinical outcomes. However, current guidelines by the American Society of Anesthesiologists Task Force on Perioperative Blood Management indicate that the overall risk of thromboembolic events following PCC transfusion is only 0.003% (evidence from observational studies).[15] Close monitoring of the PT and clinical response is recommended, with emphasis that the available evidence for using PCC in managing perioperative bleeding in patients not treated with VKA is weak (higher risk of thromboembolism is also suggested), compared with its primary indication in reversing VKA-associated bleeding.[15,20]

Cryoprecipitate

The use of cryoprecipitate (primarily to replenish fibrinogen) has been largely withdrawn by several European countries amid safety concerns, especially with regards to transmission of pathogens.[23,24] Current guidelines indicate that literature evidence is insufficient to evaluate the intra or postoperative transfusion of cryoprecipitate in the management of bleeding.[15] As a replacement, fibrinogen concentrates are increasingly used to replenish depleted fibrinogen levels.[25] FFP may also be used to supplement fibrinogen in the absence of cryoprecipitate.

Fibrinogen Concentrates

With regard to fibrinogen concentrates, there are distinct advantages over cryoprecipitate. Firstly, there is no requirement for ABO group matching.[26,27] Secondly, its administration does not involve the time delay from thawing. Thirdly, higher amounts of fibrinogen are dissolvable in small volume infusions to enable administration within a short time period and also avoid the potential of fluid overload.[27,28] The target fibrinogen level is usually set at 1 g/L, based on the literature on congenital fibrinogen deficiency,[29] but there has been a trend for earlier and higher targets of fibrinogen replacement in severe trauma.[30-33] Another advantage is in terms of viral safety because of the ability to pasteurise and filter these concentrates in the manufacturing process.[34] In a recent analysis of almost three decades of pharmacovigilance data related to fibrinogen concentrate transfusion, a small number of suspected viral transmission cases have been identified.[35] However, it was concluded that a direct causal link to fibrinogen concentrates was unlikely as polymerase chain reaction results were negative and/or alternative explanations were found.[35] As for contraindications to fibrinogen concentrate use, these include a history of anaphylactic reactions to the concentrate[36] and ongoing thrombosis or a high prothrombotic risk.[28]

In regards to approvals for the administration of fibrinogen concentrates in Europe, these are granted nationally and an approval by the European Medicines Agency (EMA) does not exist. This reflects differing strategies both to the transfusion of blood products and the approval of blood products from across European countries.

CURRENT CONCEPTS IN MONITORING COAGULATION

While most guidelines on the use of FFP and cryoprecipitate are in reference to the degree of abnormality in PT, aPTT, or fibrinogen, the availability of point-of-care testing using rotational thromboelastometry (ROTEM®) or thromboelastography (TEG®) in providing information would be important to examine for clinical value in the perioperative setting.[37] The viscoelastic properties of whole blood clot formation, as assessed by ROTEM and TEG, are dependent on thrombin-mediated fibrin formation and its polymerisation. Indeed, the extent of fibrin polymerisation as an endpoint would appear to offer an advantage because fibrin clot firmness cannot be assessed by PT, aPTT, or fibrinogen level. Different stages of ROTEM/TEG can give insights into: a decrease or inhibition of the different coagulation factors that are required for thrombin formation (early phase); the kinetic interaction of platelets and fibrin that are required for enhancing clot strength (intermediate phase); and maximum clot strength (final phase). As such, ROTEM/TEG can monitor evolving changes in the coagulation profile and identify hypofibrinogenemic, hyperfibrinolytic, and hypercoagulable states as well as the presence of low platelet/factor levels (or their inhibition).[38] This enables prompt transfusion decisions to be made, sometimes based on specific institutional algorithms, with fibrinogen concentrates, cryoprecipitate, FFP, platelets, or tranexamic acid.[38] The effect of the treatment is assessed soon after transfusion and depending on the ROTEM/TEG results, further transfusions can be tailored to the patient's specific needs. It must be emphasised that although ROTEM and TEG are based on similar principles, the results obtained with the two tests may not be interchangeable[39] because of differences in the activating reagents and operating characteristics. This may therefore result in different blood products being transfused based on which test was used.[40] It has been suggested that in the surgical setting, ROTEM may be the most appropriate test because of its faster turnaround time.[40] The new generation of viscoelastic coagulation monitoring devices with cartilage-based systems (TEG 6S, ROTEM sigma) might widen the use of these assays in the perioperative setting. The full-automation in these new devices will reduce variations in results related to pipetting, handling of blood, and prior manipulation of reagents. Finally, it must be stated that the recent European guideline for managing major bleeding and coagulopathy following trauma highlighted that the usefulness of viscoelastic tests has been questioned, and a number of significant limitations have been recently reported by several studies.[41] Therefore, the guidelines indicate that more thorough studies are required in this area and emphasise that clinicians should use judgement when designing and implementing local policies.[41]

CURRENT PERIOPERATIVE ROLE FOR COAGULATION FACTOR CONCENTRATES

Studies reviewed by Bolliger and Tanaka[42] included retrospective studies, case-control studies, and RCTs and reported that administration of fibrinogen concentrate in patients undergoing cardiac surgery

improved clot firmness, as measured by ROTEM, significantly decreased the need for other blood products such as red blood cells and FFP. Clinically, there were also significant reductions in postoperative bleeding drainage volumes. However, several important issues relevant to clinical practice were unclear; for example, FFP was often used in conjunction to make it difficult to assess the efficacy of fibrinogen concentrate alone in securing haemostasis in the bleeding patient.[29,43-45] Also, minimum core outcome sets were not defined, such as the length of follow-up for adverse clinical events and for assessing the safety of such interventions.[43-45]

More recently, two randomised double-blinded placebo-controlled trials examined the efficacy of fibrinogen concentrates in the setting of complex cardiovascular surgery.[46,47] The study by Ranucci et al.[47] found that in 116 patients, the infusion of fibrinogen concentrates (dose calculated according to fibrin–based thromboelastometry test [FIBTEM] readings) can significantly reduce subsequent allogenic blood product transfusions as compared to placebo. However, the more recent study by Rahe-Meyer et al.[46] reported an opposite result, whereby fibrinogen concentrate infusion (after a 5-minute bleeding mass of 60–250 g) resulted in increased requirement for further allogenic blood products. This discrepancy suggested that differences in the timing of transfusion, baseline fibrinogen level before transfusion, as well as variability in algorithms used to guide doses, and requirements for further transfusion[48] can have a major impact on outcomes. Although further robust RCTs are required to resolve the conflict, it must be emphasised that doses of fibrinogen concentrates as well as the requirement for other blood products are best adjusted according to the individual patient's needs. Coagulation factor concentrate therapy when coupled with point-of-care perioperative testing algorithms in a manner that is tailored to the patient's needs was found to reduce the requirement for FFP and other blood products.[49,50]

Other systematic reviews have been published in the last few years.[27,51] These have adopted a standardised analytical approach using preferred reporting items for systematic reviews and meta-analysis. The Population Intervention Comparison Outcome and Study Design (PICOS) approach was used to define inclusion. Few studies comparing FFP to fibrinogen in a perioperative or massive trauma setting[51] involved prospective high-quality methodologies. In general, fibrinogen was found to be superior to FFP for half of the outcomes that were investigated including reducing blood loss, need for allogeneic transfusions, length of intensive care unit and hospital stay, and increasing plasma fibrinogen levels.[51] However, FFP showed positive and negative effects for 28% and 22% of outcomes, respectively, with limited evidence that FFP reduced mortality.[51] In a prospective cohort study of 144 trauma patients, the use of factor concentrates (fibrinogen or PCC) alone was found to be associated with corrected coagulopathy, reduction in the need for further allogenic blood product transfusions, and reduction in the development of multiple organ failure, whereas additional FFP transfusions did not confer further haemostatic correction and were associated with higher requirement for platelets and red blood cell transfusions.[52] Collectively, this suggested that there was no strong evidence to support the clinical merit of FFP for surgical and/or massive trauma patients. Perioperatively, there was a trend towards improved outcome measures with fibrinogen concentrate treatment but solid conclusions remain difficult to draw without further robust prospective studies.[51]

Another review by Warmuth et al.[27] focussed on fibrinogen concentrate substitution in adults in the perioperative setting and with massive haemorrhage. It utilised a broader search of several databases beyond Medline, yielding 772 results between 1985 and 2010. In two RCTs and two non-RCT studies encompassing 74 patients in total, it was indicated that the administration of fibrinogen concentrate was associated with improved outcomes such as reduction in the substitution of red blood cells, FFP, and platelet concentrates as well as significantly reduced postoperative bleeding.[27] More recent systematic reviews agree that fibrinogen concentrates reduce the need for allogenic blood products transfusion in trauma and bleeding patients,[53-55] but the consensus is that the current studies are of low quality and the need for further well-designed RCTs to address the gaps in knowledge is emphasised.[53-55]

An important point to be highlighted is that some studies used maximum clot firmness as an endpoint[30] which is not a clinical outcome, but a laboratory outcome. Furthermore, Clauss fibrinogen method measurements are less sensitive to crystalloid-induced coagulation defects, whereas ROTEM is more reliable at detecting this disturbance.[56] In one study,[57] when specimens drawn from patients during major surgery were

tested in parallel using both methods, transfusion decisions based on Clauss results would result in no fibrinogen concentrate treatment in the 36 patients. Conversely, 36% of patients would have received fibrinogen concentrate if transfusion decisions were based on ROTEM guidance.[57] This stresses the critical influence of methodology on transfusion practice.

Another systematic review looked at both fibrinogen concentrates and PCC in the perioperative setting.[17] All studies included small sample sizes with highly selective inclusion criteria. However, focussing on the cardiac surgery group, prospective studies indicated that fibrinogen concentrate and/or PCC administration was associated with less allogeneic blood transfusion and reduced chest tube drainage.[17] As far as safety outcomes are concerned, it was clear that reporting was not uniform across different studies. Therefore, more robust trials with sound methodology and sufficient power are required to assess the efficacy of PCC and fibrinogen concentrates for the management of perioperative coagulopathy in bleeding patients. Finally, Table 1 provides a concise summary of the main indications for different factor-based blood products (allogenic and factor concentrates) transfusion in the perioperative setting, as adapted from current guidelines.[15]

Table 1: *Strategy for transfusion of coagulation factor concentrates in the perioperative setting.

Product	Indication for transfusion	General notes
Fresh frozen plasma	• Management of patients with severe bleeding • Reversal of VKA-associated bleeding (when PCC is not available) • Correction of specific factor deficiency (when appropriate factor concentrates are not available)	• Consider measuring PT, aPTT, and INR before FFP transfusion; viscoelastic tests may be performed
Cryoprecipitate	• Hypofibrinogenaemia • Management of patients with excessive bleeding • Management of patients with certain types of vWF and VIII deficiency (when desmopressin and/or appropriate factor concentrates are not available)	• In patients with excessive bleeding, consider measuring fibrinogen levels before cryoprecipitate transfusion. Viscoelastic tests may be performed • Desmopressin is indicated for initial management of vWF and VIII deficiency, followed by factor concentrates
Prothrombin complex concentrate	• Urgent reversal of warfarin and other VKA-associated bleeding • Patients with excessive bleeding and raised INR levels	• Little evidence is available for PCC use outside reversal of VKA-associated bleeding. Higher risk of thromboembolism is also suggested in this scenario • Optimal point-of-care testing to guide PCC administration is not available • Vitamin K may be administered in cases of non-urgent reversal of VKA-associated bleeding, except in cases where VKA is expected to commence shortly after surgery
Fibrinogen concentrate	• Hypofibrinogenaemia • Management of patients with excessive bleeding	• In patients with excessive bleeding, consider measuring fibrinogen levels before fibrinogen concentrate transfusion. Viscoelastic tests may be performed
Recombinant activated factor VII	• Management of patients with excessive bleeding when other measures (FFP, cryoprecipitate, PCC) have failed • Patients with factor VII deficiency	• Has been used in the setting of intracerebral bleeding, cerebral injury-induced coagulopathy, and in severe trauma • rFVIIa has proven value in the treatment of haemophilia patients with inhibitors

*These are general guidelines and the final decision on what and when to transfuse should always be based on careful assessment of the clinical scenario and in-line with local policies.
PT: prothrombin time; aPTT: activated partial thromboplastin time; INR: international normalised ratio; FFP: fresh frozen plasma; VKA: vitamin K antagonists; PCC: prothrombin complex concentrate; vWF: von Willebrand factor; rFVIIa: recombinant activated factor VII.

CONCLUSION

In summary, there is a need to better evidence the role of coagulation factor concentrates in the operating room to achieve optimal haemostasis and improve clinical outcome. The requirements include point-of-care tests that are simple to perform, rapid in result generation, and robust in providing an accurate status of *in vivo* coagulation. These could then lead to improved evidence and stronger transfusion guidelines that can be better standardised across Europe with wider applicability.

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GENE DELIVERY FROM STENTS FOR PREVENTION OF IN-STENT RESTENOSIS

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ABSTRACT

The increasing sophistication of vascular stent design, especially devices that combine mechanical support with local drug delivery to the vascular wall, has resulted in major progress in the management of coronary and peripheral artery disease. This progress is reflected in expanded anatomical and clinical indications for stent angioplasty, with complementary reduction in bypass surgery rates and decreased need for target-lesion revascularisation. Nevertheless, even with second-generation drug-eluting stents (DES), the most common cause of stent failure, in-stent restenosis, while <10%, generates high numbers of cases due to the large scale of stent use (there are >1 million stent angioplasty procedures yearly in the USA alone). Gene-eluting stents (GES), the next generation of stent devices now in the preclinical phase of development, have evolved over the past two decades around the concept of localised vessel wall delivery of gene vectors attached to the stent struts. GES potentially provide several important advantages over DES, such as prolonged or even permanent anti-restenotic effect, capacity to deliver dissimilar impact on smooth muscle cells and endothelium, and fine-tuning of transgene expression and pharmacological effect with systemically administered therapeutics. Furthermore, GES can be used for treating non-occlusive lesions with the aim of slowing the underlying atherosclerotic process in the vessel wall. GES research at this time is concerned with achieving effective and safe transgene overexpression in the stented arteries, optimal vector choice, and proper techniques for vector immobilisation on the stent struts.

Keywords: In-stent restenosis, gene-eluting stents (GES), drug-eluting stents (DES), gene therapy.

IN-STENT RESTENOSIS IN THE DRUG-ELUTING STENTS ERA

Percutaneous coronary interventions (PCI) utilising bare-metal stents (BMS) or drug-eluting stents (DES) are performed in >1 million patients in the USA[1] annually, to relieve atherosclerotic obstruction of coronary arteries. Although PCI immediately increases the flow across the narrowed segment, this gain is lost in a significant fraction of PCI patients due to in-stent restenosis (ISR) caused by a gradual build-up of neointima within the stented segment.[2] DES, especially second-generation devices which feature thinner struts, more biocompatible polymer coatings, and '-limus' drugs with a more appropriate pharmacological profile, achieve better long-term arterial patency than BMS and are associated with a reduced need for target-vessel revascularisation.[3] Unfortunately, the anti-restenotic effect of DES is less pronounced in patients with peripheral artery disease,[4] diabetes,[5] and renal failure.[5] While emerging third-generation stents, with completely biodegradable scaffolds or with resorbable coatings, hold promise of further incremental decrease of ISR rates, it is unlikely that ISR will be completely eliminated within the framework of DES technology.

A CONCEPT OF GENE-ELUTING STENTS

The concept of gene-eluting stents (GES) has emerged at the crossroad of vascular gene therapy and DES in an attempt to overcome some inherent deficiencies of DES. Vascular gene transfer experiments pioneered by Nabel et al.[6] provided important insights regarding the vessel

wall transducibility with viral and non-viral vectors. These studies that were largely driven by a newly described human pathology, restenosis, have also established numerous potential molecular targets for restenosis prevention.[7] Performed in the pre-stent era, initial vascular gene transfer experiments exploited a straightforward 'dwell' of gene vector suspension in the temporarily isolated arterial segment, or employed catheters allowing more precise delivery of gene therapeutics to discrete vessel compartments. Arterial tissue transduction, even with advanced catheters (double balloon, microporous, Dispatch® [SCIMED Life Sciences, Minnesota, USA], Infiltrator® [Boston Scientific, Maryland, USA), has typically remained too low for clinical translation.[8] Regardless of catheter type, the short intraluminal retention time of the delivered gene therapeutics was identified as the main reason for inadequate expression of delivered transgenes in the vasculature.[8]

Compared with the scaffold-less vascular gene delivery, stents present an advantageous physical platform for local arterial gene transfer by dramatically increasing the fraction of retained vector. Better vector retention is a combined effect of physical vector association with a permanently implanted scaffold, and a shielding effect of stent struts on the vector particles located on the stent/tissue interface. As a result, vector immobilisation on the stent requires a lower vector dose and minimises the distal spread of gene vector, thus reducing inoculation of non-target tissues. Unlike fluid-phase vector delivery, stent-based delivery is possible in the presence of side branches and does not require prolonged isolation of the treated segment, obviating procedure-related ischaemic complications. Finally, stent-based gene transfer provides an optimal spatial configuration for ISR prevention, by approximating gene vector delivery to the sites of blood-borne cell recruitment and vascular cell activation that occur predominantly around stent struts.[9]

By exploiting a more basic level of intervention (genome versus druggable proteome), GES enable conceptually novel directions for stent-based prevention and treatment of ISR. Gene therapy can attain a longer lasting therapeutic modification of vascular substrate than can be achieved through sustained drug release from DES. Gene therapy can be targeted to specific cell types, thus allowing for selective inhibition of smooth muscle cell (SMC) proliferation and migration, while sparing endothelial re-growth. A fine-tuning of delivered therapy can be achieved with 'on demand' control of therapeutic transgene expression using systemically administered drugs targeting drug-regulatable promoters.[10] Finally, by targeting a much wider range of signalling pathways, GES provide means to slow or even reverse underlying atherosclerotic processes.[11]

GENE-ELUTING STENTS TECHNOLOGIES

To date, no GES product has been evaluated in patients. The delay in clinical translation of GES is explained by the fast progress of DES technologies; by the cost and regulatory complexities of human gene therapy clinical trials; and most importantly by the remaining technical, biological, and engineering problems to be solved to fully realise GES potential. Research in the GES field has identified three major areas requiring further optimisation for moving this promising concept to clinical fruition: the nature of a therapeutic transgene, the vector type, and the delivery system (i.e. the specific way the vectors are attached to and subsequently released from the stent).

Therapeutic Transgenes

Restenosis is a multifaceted disease with a variable contribution of inflammatory, reparative, fibrotic, and foreign body responses.[2] More than 150 molecular targets are implicated in restenosis pathogenesis, thus representing potential foci for genetic interventions.[7] Only a few of these targets were investigated in conjunction with stent-based delivery in animals.

Smooth muscle cell proliferation, migration, and extracellular matrix synthesis

A common pathway of ISR pathogenesis involves phenotypic modulation of SMCs to a synthetic state, their proliferation in the media and neointima, and production of extracellular matrix (ECM). These processes which are central to neointimal tissue formation were targeted by GES in several studies. AKT1 is an important signalling intermediate of a PI3K pathway shown to convey proliferative signalling in the context of restenosis. Downregulation of *AKT1* with anti-AKT1 short-interfering RNA (siRNA)-eluting stents decreased ISR by 50% compared with BMS.[12] Stent-based delivery of an anti-sense construct to a cell cycle check-point transcription factor *c-Myc*[13] has also shown the anti-restenotic effect.

Platelet-derived growth factor (PDGF) is a prototypical SMC mitogen and chemo-attractant. An anti-sense oligodeoxynucleotide sequence complementary to the 15 base conserved coding sequence of PDGF-A isoform eluted from GES showed a profound ISR inhibition in a pig model.[14] Vascular SMC proliferation pathways are subject to post-transcriptional regulation with microRNA (miRNA). A recent study reports 70% ISR inhibition in rabbits treated with miRNA-145-eluting stents in comparison with BMS-treated animals.[15] While miRNA-145 negatively regulates SMC proliferation, expression of miRNA-21 positively correlates with neointimal mass. Accordingly, anti-miRNA-21 coated stents reduced ISR in human mammary arteries transplanted into nude rats.[16]

Matrix remodelling mediated by metalloproteases upregulated by vascular injury enables migration of SMC and myofibroblasts along the gradients of specific chemo-attractants. Stabilisation of ECM achieved with GES encoding tissue inhibitor of metalloprotease-3 reduced centripetal migration of SMC through the stented pig coronaries, and resulted in 40% ISR inhibition compared with the BMS-treated arteries.[17] Transforming growth factor-α1 (TGF-α1) is the main inductor of ECM production in vasculature. In a recent pig study, ISR was attenuated with a secreted TGF-α1 receptor-encoding GES.[18] The expressed protein acted as a decoy sequestering active TGF-α1 and reducing its downstream effects on ECM production.[18]

Enhanced endothelialisation

Early endothelialisation of denuded arteries was shown to curb neointimal formation.[19] Therefore, accelerated re-endothelialisation of stented arterial segments has been pursued as a rationale for ISR prevention. Vascular endothelial growth factor (VEGF) isoforms[20-23] and angiopoietin-1[20] were shown to be expressed following elution of respective vectors from the stent surface, with concomitant increase in endothelial re-growth and ISR inhibition in rabbit, dog, and pig models. One of these studies explored a mixed DES/GES platform and demonstrated the synergistic effect of paclitaxel/VEGF plasmid co-delivery.[23]

Nitric oxide synthesis and bioavailability

Nitric oxide (NO) is a pleiotropic regulator of vascular quiescence.[24] Fishbein et al.[25,26] and others[27-30] have investigated GES driving upregulation of NO production through the overexpression of NO synthase 2 and 3 isoforms. While generally a marked mitigation of ISR was observed in these studies, some issues remain unclear, such as the need for arginine and tetrahydrobiopterin supplementation to prevent decoupling of NO synthase,[31] and a correlation between enhanced endothelial regrowth and inhibition of restenosis.[29]

Inflammation

Chronic low-grade vascular inflammation aggravates restenosis,[32] therefore effectively curbing the inflammatory response represents a well-recognised anti-restenotic strategy.[33] In keeping with this idea, stents formulated with plasmid DNA encoding a dominant negative variant of monocyte chemo-attractant protein-1 reduced both macrophage infiltration of stented arteries and ISR in rabbit and non-human primate models.[34]

Nuclear factor kappa B (NF-κB) is a master transcription factor involved in the regulation of multiple inflammatory mediators. GES incorporating NF-κB decoy oligodeoxynucleotide deployed in femoral arteries of hypercholesterolaemic rabbits have demonstrated a 30% decrease of neointimal mass, with a concomitant decrease of inflammatory marker expression.[35]

Parietal thrombus

A non-occluding (parietal) thrombus is routinely formed at the stenting site despite antiplatelet and anticoagulant premedication. If the thrombus persists, it serves as a nidus for migrating SMC, thus facilitating neointimal expansion. Localised overexpression at the site of GES implantation of the membrane-bound enzyme ectonucleoside triphosphate diphosphohydrolase, that effectively blocks platelet aggregation, prevented thrombosis after repeated interventions in rabbit femoral arteries, and decreased the extent of restenosis at Day 7 after reintervention.[36]

Gene Vectors

Plasmid DNA possesses low transduction capacity in vascular tissue. To achieve meaningful expression levels, the therapeutic gene must be delivered in physical association with proteins, peptides, positively charged polymers, polysaccharides, or lipids, or be presented in the genome of genetically-engineered viruses. These nano-sized gene vectors provide enhanced cell entry, facilitated processing, nuclear uptake, and expression of exogenous DNA.[37] Gene vectors are categorised into viral and non-viral entities. Both types of

vectors were investigated in the context of stent-based gene transfer.

Non-viral vectors in gene-eluting stents design

The first described GES prototypes used incorporation of expression-ready plasmid DNA dispersed in poly(lactide-co-glycolide) (PLGA)[38] or collagen[39] coatings. These seminal studies demonstrated transitory reporter expression in pig arteries, yet failed to show profound effects. Denaturation of collagen increased transfection of intimal SMC 10-fold through enhancement of actin depolymerisation.[40] Other polymers, such as polyurethane,[35,41] pullulan,[42] and chitosan,[43] were used in GES for enhancing plasmid mediated transduction with demonstration of ensuing transgene expression *in vitro* and *in vivo*.

A number of reported non-viral GES platforms utilised cationic lipids alone[29,44-46] or together with cationic polymers[27,47] for condensation and protection of plasmid DNA eluted from the stent. Immobilisation of resulting lipoplexes or lipopolyplexes on stent struts was achieved with PLGA/gelatin coating,[27,47] or using several cycles of direct application of lipoplex suspension to struts of phosphorylcholine-coated stents and air drying.[22,29,44] In some studies, plasmid was anchored to the stent surface using anti-DNA antibodies prior to inducing formation of lipoplexes with Lipofectamine™ 2000 (ThermoFisher Scientific, Massachusetts, USA).[45,46] In addition to plasmids, shorter DNA and RNA constructs, negatively affecting gene expression (anti-sense, decoy, siRNA, miRNA), were delivered from polymeric stent coatings.[13,14,16,48,49]

Adenoviral vectors

Advantages of recombinant replication-deficient adenoviruses (Ad) as vectors used in GES are robust transduction of both dividing and quiescent cells, 8–34 kb capacity of transgene cassette allowing insertion of virtually any gene of interest, relative ease of high-titre production, and ability to tolerate chemical modifications. However, Ad elicit strong inflammatory and immune responses that are detrimental in the context of GES. Our group designed two prototypes of Ad-based GES, employing either non-covalent attachment of the vector via affinity adaptors[26] or covalent tethering of Ad particles through hydrolysable cross-linkers.[25] Both GES demonstrated durable reporter expression and therapeutic effectiveness in a rat model.[25,26] Several other groups also reported successful vascular gene transfer with Ad vector either immobilised on phosphorylcholine coating of BiodivYsio™ (Biocompatible Ltd., Farnham, UK) stents,[17,28,50] or on collagen membrane of CoverStent (Medtronik, Dublin, Ireland).[18]

Adeno-associated virus vectors

Currently, adeno-associated virus vectors (AAV) are the most promising viral vectors for cardiovascular gene therapy, mostly due to their well-established safety profile and minimal elicitation of inflammatory and immune response. Despite this, AAV are relatively under-investigated as the vector for GES. Sharif et al.[50] demonstrated reporter gene expression for up to 28 days using GES loaded with $5x10^9$ particles of AAV-2. However, compared to the similar amount of Ad, vector transgene expression was lower, especially in the neointima. This observation contrasts our data,[51] showing that GES constructed with AAV-9 out-performs the Ad-formulated counterparts in regards to both peak levels and the duration of expression. The difference in animal model (rat versus rabbit), AAV serotype (9 versus 2), and reporter transgene (firefly luciferase versus beta-galactosidase) may explain these divergent findings.

Recombinant baculovirus

Baculoviruses exclusively infect insect cells and thus humans do not have pre-existing neutralising antibodies to this virus. Unlike the parent virus, engineered baculoviral vectors transduce dividing and quiescent mammalian cells without eliciting marked inflammatory reactions. Recently, hybrid baculoviral vector complexed with polyamidoamine dendrimer and encapsulated into PLGA microspheres was investigated for gene transfer from a stent platform, showing uniform transduction of dog femoral arteries and therapeutic effectiveness against ISR.[20]

General Gene-Eluting Stents Design and Delivery System

Design requirements for GES delivery system have both common and unique traits compared with DES platforms. Deliverability of both types of stents should not be compromised by the accommodation of a therapeutic moiety and its matrix on the struts. The matrix deposited on struts of DES and GES has to endure the mechanical stretch during deployment without cracking or delamination, since these post-deployment defects result in irregular release rate of a therapeutic agent

and can cause embolisation of distal vasculature. Additionally, the matrix of both DES and GES needs to be highly biocompatible. Sustained release of therapeutic moiety for 3–6 months realised in most DES platforms is unnecessary for the GES, since the stent-associated cells, after being transduced with eluted vectors, will actively secrete a therapeutic product as long as they (or their progeny, in the case of genome integration) survive. An important consideration for estimating the necessary duration of vector release from GES is that neointimal SMCs (the target cell population for most GES prototypes studied to date) are not yet present at the time of vascular injury, and will start populating the intima at 7 days after stent deployment.[52] This mandates that the transduction-competent vector is released for 2–3 weeks, posing additional requirements to GES delivery system with regard to extended vector stability *in vivo*. Gene vectors are generally more vulnerable than low molecular weight drugs, and lose their activity if not properly protected by matrix interactions. Immune response to a gene vector and expressed gene product is another specific problem of GES. Therefore, preventing vector spread to regional lymph nodes, as well as physical shielding of the vector from pre-formed antibodies and effector T cells, is crucial for sustaining therapeutic levels of encoded transgene. Lastly, the one to two orders of magnitude size difference between drugs used in DES and gene vectors dictates use of different matrices to enable release.

Bulk immobilisation (polymer coatings)

The first reported GES[38,39] utilised polymer coatings on the surface of metallic stents in which gene vectors were dispersed. The coatings (typically 50–250 μm thick) were deposited on a primed stent surface either by a multiple dip technique or by aerosol deposition. After solvent evaporation and polymer precipitation on the stent surface, the gene vector stayed contained between the polymer fibres. The subsequent release of vector was then governed by a combination of diffusion though the matrix determined by hydrophilicity of the polymeric matrix and the pore size, chemical degradation of the matrix, and dissolution of the matrix in tissue fluid and blood. A variety of synthetic polymers (PLGA,[38] poly[beta-amino ester],[27,53,54] polyurethane,[35,41] poly[vinyl alcohol],[34] poly[phosphorylcholine-lauryl methacrylate][17,22,28,29,44,49,50]) and semi-synthetic polymers (dopamine-modified hyaluronic acid,[12,15,55] cationised gelatin,[36] styrene-modified gelatin,[56] cationised pullulan,[42] or naturally occurring macromolecules [native[39] or denatured[40] collagen, gelatin][27,47]) have been used for the bulk incorporation of gene vectors on stent struts.

The main advantage of bulk immobilisation is a high inclusion capacity for genetic material (up to 4 mg of plasmid DNA[41] and $5x10^{10}$ adenovector particles).[39] However, from a pharmacokinetic standpoint, the release profile of bulk immobilised vectors presents a poor match for cell dynamics in the injured vessel wall. Typically, 80–90% of the vector load is released within the first 24 hours,[17,27,34,35,42,43,49] thus missing neointimal SMC not yet present at the site of vascular injury. Rapid release of bulk-immobilised vector is mostly due to the 'burst release' of a fraction of the vector that has been absorbed onto the polymer layer after going out of solution during the solvent evaporation step. To an extent, the burst release can be counteracted using a super-coating with an additional layer of vector-free polymer,[27,38,47] or by a post-deposition polymer cross-linking.[56] Biologically, the central problem of the delivery systems based on bulk polymer coatings is inflammation in the treated arterial segment that negates the therapeutic effect of a transgene.[57]

Surface immobilisation of gene vectors on coatless metal substrate

The concept of gene vectors' immobilisation on the surface of stents directly utilises the stent surface for tethering therapeutic gene vectors in an arranged pattern to facilitate transduction of tissue on the interface with the stent.

Drug-eluting stent delivery systems based on the use of affinity binding adaptors

Studies by our group, motivated by numerous deficiencies of bulk immobilisation in the context of DES delivery systems, have investigated several strategies for reversible tethering of both viral[25,26,31,51,58] and non-viral[46] gene vectors. To chemically link the stent surface and gene vectors, we used metal surface modification with a family of poly(allylamine)-bisphosphonate (PAB) compounds that form a monolayer film (<5 nm thick) on the stent surface, through the formation of co-ordination bonds between bisphosphonic groups of PAB and metal atoms, and their oxides on the steel surface.[26] PAB can be further modified in order to provide a covalent attachment of vector binding affinity

adaptors, using N-hydroxysuccinimidyl ester-based amine conjugation and pyridyldithio-based thiol conjugation strategies.[26] High affinity vector binding proteins such as anti-Ad,[26] anti-DNA[46] antibodies, or a recombinant domain of coxsackie-adenovirus receptor[26] were used as binding adaptors, enabling high-affinity attachment of gene vectors to stents. Interestingly, both loading capacity of GES and vector release rate were shown to be modulated through using the binding adapters with different affinities to Ad vectors.[26] While fluorescently labelled Ad were observed on the interface between stent struts and the arterial wall 1 day after stent deployment, and the associated reporter (green fluorescent protein) activity was seen in all arterial layers 7 days post-stenting,[26] the release of vector *in vivo* with this affinity-based GES delivery remains poorly controllable, as the vector association with stents is determined by the antigen/antibody affinity and local pH (i.e. the factors that cannot be changed deliberately).

Gene-eluting stent delivery systems utilising hydrolysable cross-linkers

Our later work on GES delivery systems has investigated a completely synthetic approach for reversible binding of Ad vectors to metal surfaces that obviates using protein adaptors. This strategy is based on hydrolysable cross-linker molecules that directly append vectors to PAB-activated steel.[25,58] The subsequent release of the vectors is governed by the kinetics of cross-linker hydrolysis and can be modulated by the usage of hydrolysable cross-linker molecules with variable hydrolysis rates.[58] Importantly, this linking strategy allows amplification of virus binding sites on the surface (and thus increase of vector load) through the optional expansion of the thiol group number on the metal surface.[25]

Nanoparticulate delivery systems for magnetic stent targeting

Both bulk immobilisation and surface tethering strategies make use of GES delivery systems that are assembled prior to stent implantation in the artery. One potential downside of pre-made GES is that the insertion of a stent through the haemostatic valve of a vascular sheath, and its advancement to a deployment site through the narrowed arterial conduit, always involves some physical damage to the vector depot. Alternatively, a stent can be loaded with gene vectors *in situ* after implantation. The surface of a deployed stent can be actively targeted with vectors delivered to circulation, provided the targeting forces are strong enough for vectors' capture and retention despite the shearing effect of blood-flow.

This concept of a post-deployment stent loading with gene vectors was recently implemented by our group using a magnetic targeting paradigm.[59] Stents made of magnetisable alloys, when placed in a uniform magnetic field, generate strong highly-localised magnetic forces due to steep gradients of the magnetic field across the strut meshwork.[60] These magnetic forces enable the targeted capture of systemically or locally administered gene vectors formulated in a magnetically-responsive nanoparticle.[59] In our study,[59] aortic arch instillation of Ad-Luc containing magnetically-responsive nanoparticles in the presence of uniform magnetic field of 0.1 T resulted in sustained luciferase expression in the stented artery that vastly exceeded expression, following the delivery of an equal amount of free adenovector.

CONCLUSIONS

Gene delivery from the surface of an intra-arterial stent provides therapeutic opportunities for ISR prevention in clinical circumstances, where current DES devices fail to provide satisfactory results. Progress alongside the transgene/vector/delivery paradigm should determine whether GES will remain a laboratory artefact, or complement the armamentarium of clinical cardiology.

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REVOLUTION OF DRUG-ELUTING CORONARY STENTS: AN ANALYSIS OF MARKET LEADERS

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ABSTRACT

Percutaneous coronary intervention with drug-eluting stents (DES) is a well-established and widely-accepted treatment approach in patients with coronary artery disease. Although the underlying principle of DES remains constant for different stents available on the market, certain factors may offer variations with respect to deliverability (ease of placement), efficacy (preventing restenosis), and safety (thrombosis rates). These factors may include the type of drug (sirolimus, everolimus, biolimus, zotarolimus, novolimus, paclitaxel, docetaxel), type of stent platforms (stainless steel, platinum, cobalt-chromium, cobalt-nickel, platinum-chromium), type of polymers (permanent, biodegradable, polymer-free), thickness of stent struts (thick, thin, ultra-thin), type of coating (abluminal, conformal), and type of stent design (open-cell, closed-cell, combination of open-closed cell). In this context, we present a review on characteristic features of several of the most widely used coronary stents worldwide. Furthermore, the advancements of completely biodegradable stents are discussed. In addition, the future directions for the development of creating an ideal or perfect DES are debated.

Keywords: Biodegradable, bioresorbable vascular scaffold, coronary artery disease (CAD), drug-eluting stents (DES), percutaneous coronary intervention, polymer, strut, stent coating.

BACKGROUND

Coronary artery disease (CAD) is the most common cause of cardiovascular disability and death worldwide.[1] It is well established and widely accepted that percutaneous coronary intervention using coronary stents has revolutionised the treatment of CAD.[2] Since the first implantation of a coronary stent in 1986 and the first US Food and Drug Administration (FDA) approval for a coronary stent in 1994,[3] medical and technological advances have brought pioneering transformations. These include the establishment of newer stent designs and the development of a variety of coronary stents, including bare-metal stents, drug-eluting stents (DES), and fully bioabsorbable stents.[4]

Bare-metal coronary stents made of stainless steel, cobalt, chromium, or other metals were the first introduced to the market. Although bare-metal stents are still used in some centres, significant concerns remain regarding the high risk of restenosis and stent thrombosis. Here, restenosis occurs mainly due to proliferation of neointimal hyperplasia of smooth muscle cells after stent implantation. In order to overcome these challenges, DES containing anti-restenotic or anti-proliferative agents were developed. These DES provide local, site-specific, controlled release of an anti-restenotic drug that can inhibit neointima formation.[5] These stents have demonstrated reduced clinical and angiographic revascularisation rates when compared to bare-metal stents in various randomised controlled trials and post-marketing surveillance registries.[6-11] Subsequent developments in anti-restenotic agents, polymeric coatings, and improvised stent platforms have further reduced the risk of these complications.[5] Nevertheless, once thought to be the solution for restenosis, DES are

now faced with their own challenges of late stent thrombosis. This has renewed interest in designing a better coronary stent.[12] First-generation DES include sirolimus-eluting stents (2003) and paclitaxel-eluting stents (2004), while the second-generation DES include zotarolimus-eluting stents (2008) and everolimus-eluting stents (2008), with permanent polymer coatings.[5] Newer-generation stents, including stents with biodegradable polymers, polymer-free stents, and biodegradable stents, are the novel frontiers. While the safety and efficacy of the majority of these stents are supported by respective clinical trials and registries, larger trials and longer follow-ups are necessary to assess their long-term effectiveness.[13]

The safety and efficacy of these DES are usually evaluated in clinical trials and registries in terms of major adverse cardiac events (as a composite of cardiac death, myocardial infarction, and repeat revascularisation) and stent thrombosis.[14] Here it should be noted that the cause of these adverse outcomes could be multifactorial.[15] Although the underlying principle of DES remains constant for different stents available on the market, certain factors may offer variations with respect to deliverability (ease of placement), efficacy (preventing restenosis), and safety (thrombosis rates). Apart from patient characteristics and lesion complexity, stent design and stent composition are identified as important factors which may influence clinical outcomes.[16] In brief, these factors, shown in Figure 1, include the type of drug (sirolimus, everolimus, biolimus, zotarolimus, novolimus, paclitaxel, docetaxel), type of stent platforms (stainless steel, platinum, cobalt-chromium, cobalt-nickel, platinum-chromium), type of polymers (permanent, biodegradable, polymer-free), thickness of stent struts (thick, thin, ultra-thin), type of coating (abluminal, conformal), and type of stent design (open-cell, closed-cell, hybrid).

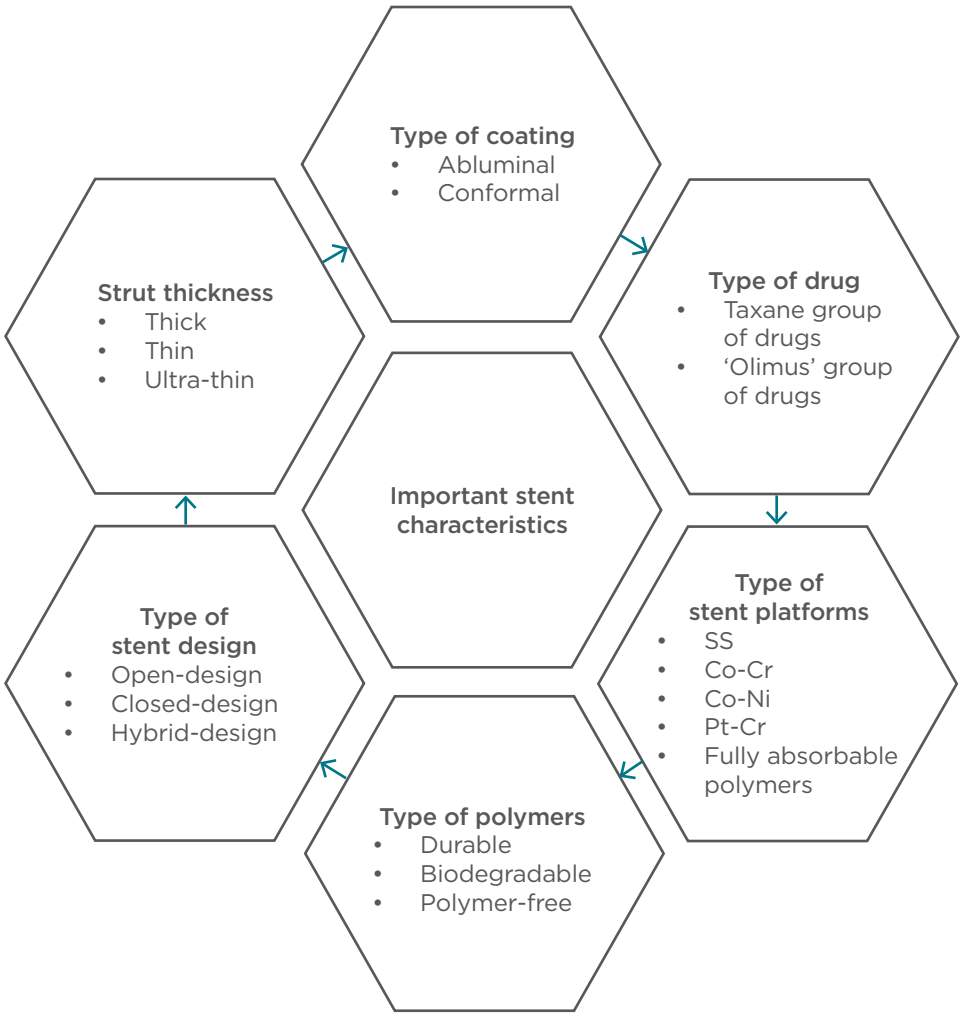

Figure 1: Important characteristics of coronary stents that can influence clinical outcomes.
SS: stainless steel; Co-Cr: cobalt-chromium; Co-Ni: cobalt-nickel; Pt-Cr: platinum-chromium.

Table 1: Appraisal of design-related characteristics of most widely-used coronary drug-eluting stents.

Stent name	Manufacturer	Drug (dose)	Polymer	Biocompatibility	Polymer thickness (μm)	Stent platform	Strut thickness (μm)
Axxion™	BioSensors International (Boon Lay, Singapore)	Paclitaxel	None	None	-	Stainless steel	119
Taxus Express²™	Boston Scientific (Marlborough, MA, USA)	Paclitaxel (1 μg/mm²)	Translute SIBS copolymer	Durable	16	Stainless steel	132
Taxus Liberté™	Boston Scientific (Marlborough, MA, USA)	Paclitaxel (1 μg/mm²)	Translute SIBS copolymer	Durable	16	Stainless steel	97
Ion™	Boston Scientific (Marlborough, MA, USA)	Paclitaxel (1 μg/mm²)	Triblock copolymer*	Durable	-	Stainless steel platinum-chromium	81–86
Promus™	Boston Scientific (Marlborough, MA, USA)	Everolimus (1 μg/mm²)	PBMA, PVDF-HFP (Fluoropolymer)	Durable	7.6	Cobalt-chromium	81
Promus™ Element™	Boston Scientific (Marlborough, MA, USA)	Everolimus (1 μg/mm²)	PBMA, PVDF-HFP (Fluoropolymer)	Durable	7.0	Platinum-chromium	81
Synergy™	Boston Scientific (Marlborough, MA, USA)	Everolimus (1 μg/mm²)	PLGA	Biodegradable	4	Platinum-chromium	74
Xience V®/ Xience Prime®/ Xience Alpine®/ Xience Xpedition®	Abbott Vascular (Green Oaks, IL, USA)	Everolimus (1 μg/mm²)	PBMA, PVDF-HFP (Fluoropolymer)	Durable	7.6	Cobalt-chromium	81
Cypher®	Cordis Corporation (Baar, Switzerland)	Sirolimus (1.4 μg/mm²)	PEVA + PBMA	Durable	12.6	Stainless steel	140
Cypher Select®	Cordis Corporation (Baar, Switzerland)	Sirolimus (1.4 μg/mm²)	PEVA + PBMA	Durable	-	Stainless steel	100
BioMime™	Meril Life Sciences (Gujarat, India)	Sirolimus (1.25 μg/mm²)	PLLA + PLGA	Biodegradable	2	Cobalt-chromium	65
Orsiro	Biotronik (Bülach, Switzerland)	Sirolimus	Dual-polymer mix†	Biodegradable	7.4	Cobalt-chromium	60–80
Coroflex® ISAR	B. Braun Melsungen (Hessen, Germany)	Sirolimus	None	None	N/A	Cobalt-chromium	60
Ultimaster®	Terumo (Tokyo, Japan)	Sirolimus	poly(dl-lactide-co-caprolactone)	Biodegradable	-	Cobalt-chromium	80
Yukon Choice® PC	Translumina Therapeutics (New Delhi, India)	GmbH Sirolimus	PLA + shellac resin	Biodegradable	-	Stainless steel	87
Yukon Choice® Flex	Translumina Therapeutics (New Delhi, India)	GmbH Sirolimus	PLA + shellac resin	Biodegradable	-	Cobalt-chromium	79

Table 1 continued.

Stent name	Manufacturer	Drug (dose)	Polymer	Biocompatibility	Polymer thickness (μm)	Stent platform	Strut thickness (μm)
Cre8™	Alvimedica (Istanbul, Turkey)	Amphilimus (Sirolimus + organic acid) (0.9 μg/mm²)	None	None	-	Cobalt-chromium	80
BioFreedom™	BioSensors International (Boon Lay, Singapore)	Biolimus A9	None	None	-	Stainless steel	
BioMatrix™	BioSensors International (Boon Lay, Singapore)	Biolimus A9	PLA	Biodegradable	10	Stainless steel	112–137
Nobori®	Terumo (Tokyo, Japan)	Biolimus A9	PLA	Biodegradable	20	Stainless steel	120
Endeavor®	Medtronic (Dublin, Ireland)	Zotarolimus (1 μg/mm²)	Phosphorylcholine	Durable	4.3	Cobalt-chromium	91
Endeavor Resolute™	Medtronic (Dublin, Ireland)	Zotarolimus (1 μg/mm²)	Biolinx‡	Biocompatible	5.6	Cobalt-chromium	81
Resolute Integrity®	Medtronic (Dublin, Ireland)	Zotarolimus (1 μg/mm²)	Biolinx‡	Biocompatible	6	Cobalt-chromium	91
Resolute Onyx™	Medtronic (Dublin, Ireland)	Zotarolimus (1 μg/mm²)	Biolinx‡	Biocompatible	-	Cobalt-chromium	81
DESolve	Elixir Medical (Sunnyvale, CA, USA)	Myolimus	Methacrylate	Durable	<3	Cobalt-chromium	81
DESyne® NOVOLIMUS™	Elixir Medical (Sunnyvale, CA, USA)	Novolimus	Methacrylate	Durable	3	Cobalt-chromium	81

*Polystyrene and polyisobutylene.
†passive coating of PROBIO (amorphous silicon carbide) and active coating of BIOlute (PLLA).
‡composed of hydrophobic C10, hydrophilic C19, and polyvinyl pyrrolidone.
PBMA: poly(methacryloyl β-alanine); PVDF-HFP: polyvinylidenefluoro-hexafluoropropylene; PEVA: polyethylene-co-vinyl acetate; PLA: poly(lactic acid); PLGA: poly(dl-lactic-co-glycolic acid); PLLA: poly(L-lactic acid); SIBS: styrene-isobutylene-styrene.

With this background, we scrutinised the available published literature on DES for the present review. The search engines included PubMed, ScienceDirect, and Google Scholar. Accordingly, the most widely described coronary stents were identified and examined for their characteristics, including stent design, strut thickness, stent platform, use of polymers, and the choice of anti-restenotic drug (Table 1). Furthermore, the advancements in completely biodegradable stents are discussed (Table 2). In addition, future directions for the development of an ideal or perfect DES are debated.

ANTI-PROLIFERATIVE DRUG

The DES system is often distinguished by the anti-proliferative drug applied to the stent. FDA-approved first-generation DES, such as the Cypher® sirolimus-eluting stent (Cordis Corporation, Baar, Switzerland) and the Taxus® Express²™ paclitaxel-eluting stent (Boston Scientific, Marlborough, Massachusetts, USA) demonstrated promising results compared to bare-metal stents.[6-9] However, these stents displayed potential for increased inflammation, delayed healing, and late stent thrombosis, which could not be ignored.

Table 2: Appraisal of design-related characteristics of fully bioabsorbable/bioresorbable coronary stents/scaffolds.

Stent name	Manufacturer	Strut material	Coating material	Eluted drug	Strut thickness (μm)	Resorption time (months)
Igaki-Tamai®	Kyoto Medical Planning (Kyoto, Japan)	PLLA	None	None	170	24–36
REVA	REVA Medical (San Diego, CA, USA)	PTD-PC	None	None	200	24
ART 18AZ	Arterial Remodeling Technologies (ART) (Paris, France)	PDLLA	None	None	170	18–24
FADES®	Zorion Medical (Zionsville, IN, USA)	Magnesium alloy + PLGA	None	None	-	6
Fortitude®	Amaranth Medical (Mountain View, CA, USA)	Semicrystalline polylactide	None	None	150–200	3–6
Amaranth BRS	Amaranth Medical (Mountain View, CA, USA)	PLLA	None	None	156	12–24
DREAMS Absorbable Magnesium Scaffold (AMS)	Biotronik (Bülach, Switzerland)	Magnesium alloy	None	None	165	<4
DREAMS-1	Biotronik (Bülach, Switzerland)	Magnesium alloy	PLGA	Paclitaxel	125	9
DREAMS-2	Biotronik (Bülach, Switzerland)	Magnesium alloy	PLLA	Sirolimus	150	9
MeRes 100™	Meril Life Sciences (Gujarat, India)	PLLA	PDLLA	Sirolimus	100	24–36
ReZolve®	REVA Medical (San Diego, CA, USA)	PTD-PC	None	Sirolimus	114–228	24
ReZolve®2	REVA Medical (San Diego, CA, USA)	PTD-PC	None	Sirolimus	100	48
Fantom®	REVA Medical (San Diego, CA, USA)	PTD-PC	None	Sirolimus	125	36
Mirage Bioresorbable Microfiber Scaffold	Mirage BRMS, Manli Cardiology Singapore	PLLA	None	Sirolimus	125–150	14
Xinsorb	HuaAn Biotechnology (Laiwu, China)	PLLA + PAL + PCL + PLGA	PDLLA	Sirolimus	160	24–36

Table 2 continued.

Stent name	Manufacturer	Strut material	Coating material	Eluted drug	Strut thickness (μm)	Resorption time (months)
BTI scaffold	Bioabsorbable Therapeutics Inc. (Menlo Park, CA, USA)	Polymer salicylate + linker	Salicylate + different linker	Sirolimus	200	12
IDEAL™ Biostent	Bioabsorbable Therapeutics Inc. (Menlo Park, CA, USA)	Polymer salicylate + linker	Salicylate + different linker	Sirolimus	175	12
Acute	OrbusNeich (Wan Chai, Hong Kong)	PCL + PDLLA + PLLA	None	Sirolimus + CD34	150	Under investigation
Absorb™ Bioresorbable Vascular Scaffold 1.1	Abbott Vascular (Green Oaks, IL, USA)	PLLA	PDLLA	Everolimus	156	24–36
DESolve	Elixir Medical (Sunnyvale, CA, USA)	PLLA	None	Myolimus	150	12–24
DESolve 100® Novolimus	Elixir Medical (Sunnyvale, CA, USA)	PLLA	PLLA	Novolimus	100	24

PTD-PC: polytyrosine derived polycarbonate; PAL: poly(aspartic acid-co-lactide), PCL: poly(ε-caprolactone); PLLA: poly(L-lactic acid); PDLLA: poly(dl-lactide acid); PLGA: poly(dl-lactic-co-glycolic acid).

This prompted the development of next-generation stents. Subsequently, many drugs have been proposed and/or tested to reduce neointimal hyperplasia and/or inflammation with DES.[17]

Overall, two major classes of anti-proliferative drugs are used in DES. The 'olimus' group of drugs (i.e. sirolimus, everolimus, biolimus, and zotarolimus) act on the mammalian target of rapamycin, a key intermediary in the phosphatidylinositol 3-kinase pathway,[18] while the taxane group of drugs (i.e. paclitaxel, docetaxel) acts downstream of these pathways by inhibiting microtubular function, which is required for cell migration and proliferation.[19] Numerous clinical studies have verified the safety and efficacy of:[20-33]

- Paclitaxel-eluting stents (Taxus Liberté™ and Ion™, Boston Scientific; Axxion™, Biosensors International, Boon Lay, Singapore)
- Sirolimus-eluting stents (BioMime™, Meril Life Sciences, Gujarat, India; Cypher, Cordis Corporation; Yukon® Choice PC, Translumina Therapeutics, New Delhi, India; Orsiro, Biotronik, Bülach, Switzerland; Coroflex® ISAR, B. Braun, Hessen, Germany; Ultimaster®, Terumo Corporation, Tokyo, Japan)

Other 'olimus'-eluting drugs are widely used in current interventional cardiology practice, including:[20-33]

- Everolimus (Xience V®, Abbott Vascular, Green Oaks, Illinois, USA; PROMUS™ and Synergy™, Boston Scientific)
- Zotarolimus (Endeavor®, and Resolute™ Integrity, Medtronic, Dublin, Ireland)
- Biolimus A9 (BioMatrix™ and BioFreedom™, Biosensors International; Nobori®, Terumo Corporation)
- Myolimus (DESolve I, Elixir® Medical, Sunnyvale, California, USA)
- Novolimus (DESyne®, Elixir Medical)
- Amphilimus (a sirolimus formulated with a polymer-free amphiphilic carrier; Cre8™, Alvimedica, Istanbul, Turkey)

Numerous trials have compared the safety and efficacy of these DES to identify an appropriate stent with better outcomes. However, sirolimus-eluting stents have shown a significantly lower risk of restenosis and target-vessel revascularisation compared with paclitaxel-eluting stents in meta-analyses of randomised trials.[34-36] Additionally, the in-stent late loss and in-stent diameter stenosis

at 1 year were lower with sirolimus-eluting stents when compared with paclitaxel-eluting stents.[36] Similarly, sirolimus-eluting stents, in comparison with zotarolimus-eluting stents, have shown better clinical outcomes in terms of restenosis, target-lesion revascularisation, and target-vessel revascularisation.[37] Furthermore, a recent meta-analysis of five randomised trials reported that everolimus-eluting stents and sirolimus-eluting stents have comparable outcomes.[38] Amphilimus-eluting coronary stents have also shown promising preliminary results in diabetic patients.[28] It should be noted that the selection of appropriate anti-proliferative agents among various DES could be a key determinant factor in percutaneous coronary intervention outcomes.

STENT PLATFORM

DES platforms must have:

- A low crimped profile
- High flexibility
- Excellent trackability
- High deliverability
- Minimum shortening during expansion
- Good conformability upon deployment
- High radial strength
- Minimal radial recoiling[26]

In the majority of conventional DES, either stainless steel or cobalt-chromium alloys are used as the metal platform. These metals exhibit reasonably good behavioural profiles in terms of biocompatibility, fatigue testing, and fracture.[27] While stainless steel alloys offer favourable vascular biocompatibility, visualisation under x-ray fluoroscopy is challenging, especially with thin-strut design stents.[39] In this regard, cobalt-chromium alloys offer superior benefits by providing denser metal and by allowing thinner struts, which may enhance acute stent performance while retaining adequate radiopacity.[22,27] Several other radiopaque materials such as tantalum or gold were initially explored; however, the clinical data indicated increased restenosis and mortality risk with gold-coated stents.[39] Recently, platinum-chromium metal based stent platforms have been developed, which seems to be an attractive metal compound for stent alloys owing to its superior strength, fracture resistance, chemical stability, and biocompatibility.[40] Furthermore, the radiopacity of platinum-chromium is higher, allowing the use of thinner struts without sacrificing visibility.[39] Another revolution in stent platform comprises the development of nickel-titanium (nitinol)-based self-expanding coronary stents.[22] Since radiographic visibility of the stent is an important feature associated with procedural outcomes, the majority of stents offer two radiopaque markers at the two stent edges to help make the stent implantation more predictable and controllable.[29,33]

The stainless steel platform based DES include Axxion (Biosensors International), Taxus Liberté (Boston Scientific), Cypher (Cordis Corporation), Yukon Choice PC (Translumina), BioMatrix (Biosensors International), BioFreedom (Biosensors International), and Nobori (Terumo). The cobalt-chromium based DES include BioMime (Meril Life Sciences), Promus (Boston Scientific), Xience V, Endeavor (Medtronic), Orsiro (Biotronik), Elixir (Elixir Medical), Cre8 (Alvimedica), Coroflex ISAR (B. Braun), and Ultimaster (Terumo). The platinum-chromium based DES include PROMUS™ Element™ and Synergy (Boston Scientific).[20,22,27-32]

STENT DESIGN

Stent design plays an important role in providing flexibility, deliverability, adequate scaffolding, and radial hoop strength. In recent years, the stent designs have evolved significantly. In the majority of currently used stents, the stent design comprises either an open-cell structure (e.g Xience V and MULTI-LINK VISION®, Abbott Vascular; Endeavor and Driver®, Medtronic; Taxus Liberté and Express™, Boston Scientific; Cre8, Alvimedica) or undulating longitudinal connectors with a closed-cell structure (e.g. Cypher and Bx Velocity®, Cordis Corporation) to connect the expandable circumferential slotted structures.[27,28] In closed-cell design, all internal inflection points of the structural members are connected by bridging elements. This offers advantages of optimal scaffolding and a uniform surface, regardless of the degree of bending. However, stents with closed-cell designs are reported to be less flexible than a similar stent with an open-cell design.[41] On the other hand, closed-cell stent designs are reported to have less plaque prolapse and have improved drug-delivery distribution.[27] While the open-cell design facilitates access to side branches and the possibility to pen the side-stent struts of the stent, the closed-cell design does not allow significant expansion of the opening toward the side branch even after crossing and inflating a balloon.[33] Considering these

factors, a hybrid-cell structure comprising a mix of open-cell stent design in the mid segments and closed-cell design at the edges has been developed in recent years. These stents (e.g. BioMime) may offer the advantages of high radial strength (due to closed-cell design at the edges) and the benefits of improved conformability and side branch access (due to open-cell design in the mid segments).[41] The stent design may play a vital role in treating bifurcation lesions.

STRUT THICKNESS

In addition to the stent design and type of metal used, the strut thickness may significantly affect vascular response.[42] It has been postulated that a wide strut can contribute to increased rates of periprocedural myocardial infarction, either by distal embolisation or by completely covering a side branch that is no longer accessible with a wire.[43] On the other hand, thinner struts may offer lower restenosis rates and improved healing, possibly due to less stent-induced arterial injury, lessened inflammation, and lessened neointimal hyperplasia.[42,43] Clinical studies have also demonstrated that reduced strut thickness results in lower restenosis rates after stent placement.[44,45] Thinner struts also result in improved stent deliverability, increased flexibility, and allow lower-pressure deployment.[15]

The majority of currently available commercial coronary stents have a strut thickness <100 μm. However, the first-generation stainless steel based coronary stents have a strut thickness of 132 μm (Taxus Express^2) to 140 μm (Cypher, BX Velocity). Subsequent medical advances with the use of stronger and more radiopaque metals such as cobalt-chromium and platinum-chromium, have allowed the incorporation of thinner struts without sacrificing strength or visibility. Currently available stents with thinner strut thickness (60–97 μm) are shown in Table 3. Overall, it should be noted that thinner struts may provide significant advantages with regard to acute stent performance characteristics.[27,42]

POLYMER

There is strong evidence to suggest that the use of polymers in stents may influence the incidence of late and very late stent thrombosis and, subsequently, this has become a fundamental area for new research and stent development.[15] The initially developed major DES systems used biostable or non-biodegradable polymers.

Table 3: Currently available drug-eluting coronary stents with thinner strut thickness.[23,27-31,39]

Manufacturer	Product	Strut thickness (μm)
Boston Scientific (Marlborough, MA, USA)	Taxus™ Liberté™	97
Medtronic (Dublin, Ireland)	Endeavor®	91
Translumina Therapeutics (New Delhi, India)	Yukon® Choice PC	87
Boston Scientific (Marlborough, MA, USA)	Ion™	81–86
Boston Scientific (Marlborough, MA, USA)	Promus™	81
Boston Scientific (Marlborough, MA, USA)	Promus Element™	81
Abbott Vascular (Green Oaks, IL, USA)	Xience V®	81
Abbott Vascular (Green Oaks, IL, USA)	Xience Alpine®	81
Medtronic (Dublin, Ireland)	Resolute	81
Medtronic (Dublin, Ireland)	Resolute Onyx™	81
Elixir Medical (Sunnyvale, CA, USA)	DESyne®	81
Alvimedica (Istanbul, Turkey)	Cre8™	80
Terumo EMEA (Leuven, Belgium)	Ultimaster®	80
Translumina Therapeutics (New Delhi, India)	Yukon® Choice Flex	79
Boston Scientific (Marlborough, MA, USA)	Synergy™	74
Meril Life Sciences (Gujarat, India)	BioMime™	65
Biotronik (Bülach, Switzerland)	Orsiro	60–80
B. Braun Melsungen (Hessen, Germany)	Coroflex® ISAR	60

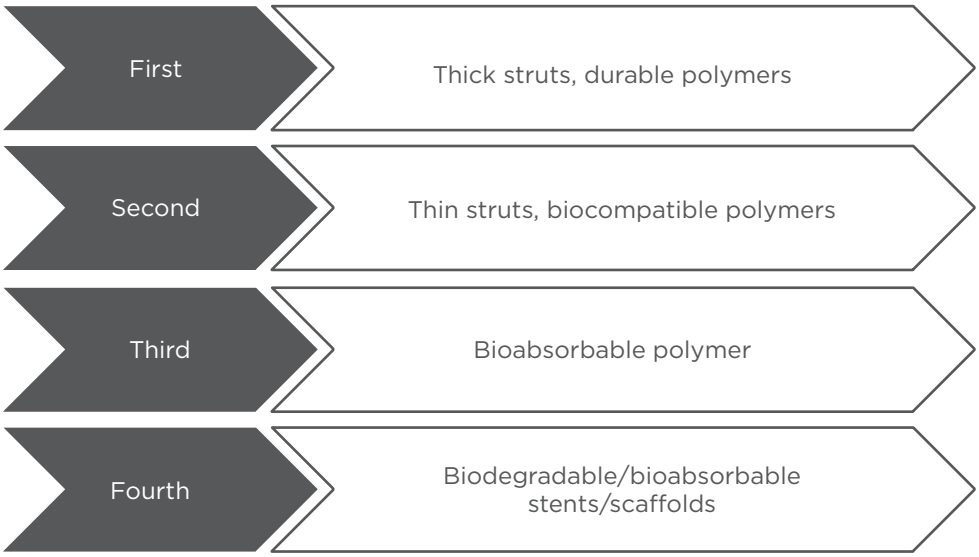

Figure 2: Differences between the first, second, third, and fourth-generation of drug-eluting stents.

The Cypher DES elutes sirolimus from a polyethylene-co-vinyl acetate/poly N-butyl methacrylate polymer, while the Taxus Express[2] elutes paclitaxel from a styrene-isobutylene-styrene polymer.[27] Subsequently developed stents with biostable polymers include the Endeavor DES system that elutes zotarolimus from phosphrylcholine polymer and the Xience V DES system that elutes everolimus from flouropolymer.[46] The advantages of using biostable polymers include the controlled release of the drug, uniform drug delivery, and a longer shelf-life. However, the utility of biostable polymers in the stent system negatively affects the long-term clinical outcomes as presence of the polymer, even after the drug has been eluted, stimulates local inflammatory reaction and delays healing of affected arteries.[47] Accordingly, stents with these biostable polymers possess high risk of late restenosis and very late stent thrombosis.[27] This has led to the development of DES coated with biodegradable polymers, offering the clinical advantages of controlled-drug release along with biodegradation of the polymers.[15]

Using biodegradable polymers such as polylactic-co-glycolic acid (or others) in the stent system is appealing because the drug-elution is completed along with the bioabsorption of the polymer drug carrier. This would reduce local inflammatory reaction and irritation, leaving only the metal stent in adhesion with neointima and endothelium, thereby reducing the long-term risks associated with the presence of a permanent polymer. Thus, the coronary stent systems with biodegradable polymers may offer the benefits of anti-restenotic efficacy of standard DES in the initial period, when the risk of restenosis and stent thrombosis is high, whereas once the polymer has biodegraded, it may offer the safety benefits of a bare-metal stent.[15,48] Currently, DES such as BioMime, BioMatrix, Nobori, Yukon® Choice Flex, Synergy, and Orsiro have anti-proliferative drugs coated along with biodegradable polymers. These stents have shown encouraging results in various clinical studies.[49-51]

The recent revolution in the field of interventional cardiology includes the use of metallic stent structures with porous surfaces, allowing appropriate drug-elution kinetics without the use of a polymer.[52] This approach could be clinically beneficial if the optimal dosing and pharmacokinetics of the anti-proliferative drug can be achieved with it. Currently, the DES that use a non-polymer approach include Biolimus A9® DES system (Biosensors International) with biolimus drug, VESTAsync™ DES system (MIV Therapeutics, Surat, Gujarat, India), Coroflex ISAR DES system (B. Braun), and BioFreedom DES system (Biosensors International) with hydroxyapatite releasing sirolimus, and Cre8 DES system (Alvimedica) with amphilimus drug.[27-32]

TYPE OF COATING

The type of coating on each DES may also play a key role.[5] Between the two types, conformal

coating inhibits smooth cell proliferation all over the stent surface, while abluminal coating will only have an effect on the outer surface of the stent (i.e. opposite to luminal side), which may contribute to the risk of increased neointimal thickness over the luminal surface. Hence, theoretically, conformal coating scores over abluminal coating. Currently available DES systems with abluminal coating include Biomatrix, Nobori, Elixir, Cre8, and Orsiro, while the DES systems with conformal coating include Xience V, Endeavor, and BioMime. In addition, the thickness of the coating is also considered to play an important role in clinical outcomes. It is desirable to have a thinner homogenous coating on the surface of DES.[15,29]

FULLY BIOABSORBABLE DRUG-ELUTING STENTS

Fully biodegradable or bioabsorbable stents/scaffolds, made of polymers or metal alloys with or without a drug coating, have been developed with an aim to provide immediate scaffolding to the stenosed artery, followed by complete biodegradation of the stent/scaffold within 6 months to 2 years, leaving behind a naturally healed similar vessel.[26,27] The concept of a fully bioabsorbable stent/scaffold was established with the fact that the long-term placement of a bare-metal stent in the vessel wall would be inflammatory and leads to inevitable restenosis. Thus, fully bioabsorbable stents/scaffolds may reduce the chronic inflammation associated with a metallic platform.[27] Such stents/scaffolds would also prevent the need for long-term antiplatelet therapy. Future surgical options will not be restricted as no foreign material would be left behind.[26] However, fully bioabsorbable stents/scaffolds are associated with certain challenges. The major problems associated with fully bioabsorbable stents/scaffolds include early stent absorption, leading to the loss of scaffolding and allowing late loss, and a greater degradation rate of polymer as compared with a metallic structure, potentially leading to long-term adverse effects due to inflammation. Other concerns include flexibility, deliverability, vascular compatibility, and radial hoop strength.[39]

In general, there are two types of fully bioabsorbable stents/scaffolds: those made from organic biopolymers and those made from corrodible metals.[26] The currently available fully bioabsorbable stents/scaffolds include:

- Everolimus-eluting bioresorbable vascular scaffold Absorb™ (Abbott Vascular)
- Sirolimus-eluting bioresorbable vascular scaffold MeRes 100™ (Meril Life Sciences)
- Sirolimus salicylate-eluting The IDEAL™ stent (Bioabsorbable Therapeutics Inc, Menlo Park, California, USA)
- Novolimus-eluting bioresorbable coronary scaffold DESolve® 100 Novolimus (Elixir Medical)
- High molecular weight poly-L-lactic acid (PLLA)-based Igaki-Tamai® stent (Kyoto Medical Planning, Kyoto, Japan)
- DRug Eluting Absorbable Metal Scaffold (DREAMS) absorbable magnesium scaffold (Biotronik)
- Tyrosine polycarbonate polymer-based REVA stent (REVA Medical, San Diego, California, USA)

Clinical studies have shown favourable efficacy and safety with fully bioabsorbable stents/scaffolds in CAD patients.[53-60]

THE PURSUIT FOR AN IDEAL DRUG-ELUTING STENT

The major differences between the first, second, third, and fourth-generations of DES are depicted in Figure 2.[61] Although considerable advances have been made in platform, drug, and polymer technology since the introduction of the first-generation DES, the pursuit for an ideal DES is still ongoing. Extensive worldwide research is focussing on further optimisation of stent design to incorporate thinner struts, reduced use of durable polymers, and combination therapies to inhibit restenosis, while promoting endothelialisation and reducing dependence on dual antiplatelet therapy.[39] In addition, there is a need to develop DES that are customised to treat specific patient profiles such as those with diabetes, small vessels, bifurcation lesions, long lesions, or tapered lesions. One such revolution in this regard is the development of BioMime™ Morph sirolimus-eluting stent (Meril Life Sciences) for the management of patients with long tapered lesions.

Overall, it can be postulated that the ideal DES should most likely incorporate a number of newer and improved materials and delivery systems to further enhance safety, efficacy, and cost-efficiency. The characteristic features of the ideal DES system may include:[27]

- Eluting an 'olimus' drug (e.g. sirolimus, everolimus, biolimus A9, myolimus, novolimus)
- High flexibility and high conformability (hybrid open-cell design)
- Adequate radiopacity and radial strength (metallic platform)
- A very thin (homogeneous) surface of bioabsorbable (non-inflammatory) polymer
- Thinner struts
- Stimulation of early re-endothelialisation
- A thrombus-resistant luminal surface
- A very low-profile stent delivery system
- A high-pressure balloon (suitable for direct stenting)
- Drug-elution for about 60–90 days, followed by complete absence of drug release
- Minimising the need for antiplatelet treatment for ≤3 months
- Minimal late loss (≤0.2 mm)

SUMMARY

The present review reports development and revolution in coronary DES technology, with major emphasis on advancements in the type of drug used (sirolimus, everolimus, biolimus, zotarolimus, novolimus, paclitaxel, docetaxel); type of stent platforms (stainless steel, platinum, cobalt-chromium, cobalt-nickel, platinum-chromium); type of polymers (permanent, biodegradable, polymer-free); thickness of stent struts (thick, thin, ultra-thin); type of coating (abluminal, conformal); and type of stent design (open-cell, closed-cell, combination of open-closed cell). Although considerable advances have been made, the pursuit for an ideal DES system is still ongoing. While the safety and efficacy of a majority of the contemporary stents on the market are supported by respective clinical trials and registries, larger trials and longer follow-ups are necessary to assess the effectiveness of certain novel devices. Overall, it can be concluded that DES will continue to play a prominent role in the management of patients with CAD.

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