EMJ HEMATOLOGY

Vol. 9.1 August 2021 emjreviews.com

EHA2021 Virtual Congress

EDITOR'S PICK

Von Willebrand Factor and ADAMTS13 in COVID-19 and Beyond: A Question of Balance

INTERVIEWS

Interviews with Ruud Delwel and Nikhil Munshi

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Editorial Board

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Aims and Scope

EMJ is an online only, peer-reviewed, open access general journal, targeted towards readers in the medical sciences. We aim to make all our articles accessible to readers from any medical discipline.

EMJ allows healthcare professionals to stay abreast of key advances and opinions across Europe.

EMJ aims to support healthcare professionals in continuously developing their knowledge, effectiveness, and productivity. The editorial policy is designed to encourage discussion among this peer group.

EMJ is published quarterly and comprises review articles, case reports, practice guides, theoretical discussions, and original research.

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Staff members attend medical congresses as reporters when required.

This Publication

ISSN 2053-4248

EMJ Hematology is published once a year. For subscription details please visit: www.emjreviews.com

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EMJ Hematology 9.1

Welcome

Dear Readers,

We are delighted to welcome you to the latest issue of *EMJ Hematology*. Included in our newest eJournal is an exciting range of content, including peer-reviewed articles, an independent review of the European Hematology Association (EHA) 2021 Virtual Congress, interviews with experts in the field, and abstract summaries from EHA 2021 to share the latest haematology updates. We are eager to highlight up-to-date scientific developments in haematology, maintaining our goal to offer the finest-quality content and stimulate ground-breaking studies in the future.

The peer-reviewed articles that you will find within this issue cover topics including managing multiple myeloma in older patients, a review of recent and forthcoming advances in the treatment of thalassaemia, and a rare case of Glanzmann thrombasthenia. The Editor's Pick this issue is the interesting narrative review 'Von Willebrand Factor and ADAMTS13 in COVID-19 and Beyond: A Question of Balance' by Favaloro et al.

We had the pleasure of attending another excellent EHA congress. Despite being in an online environment, EHA 2021 continued to provide high-quality content, bringing haematologists together for the latest updates in the field. Also shared in this issue is an exclusive congress committee interview with Ruud Delwel, Chair of Scientific Program Committee, EHA 2021.

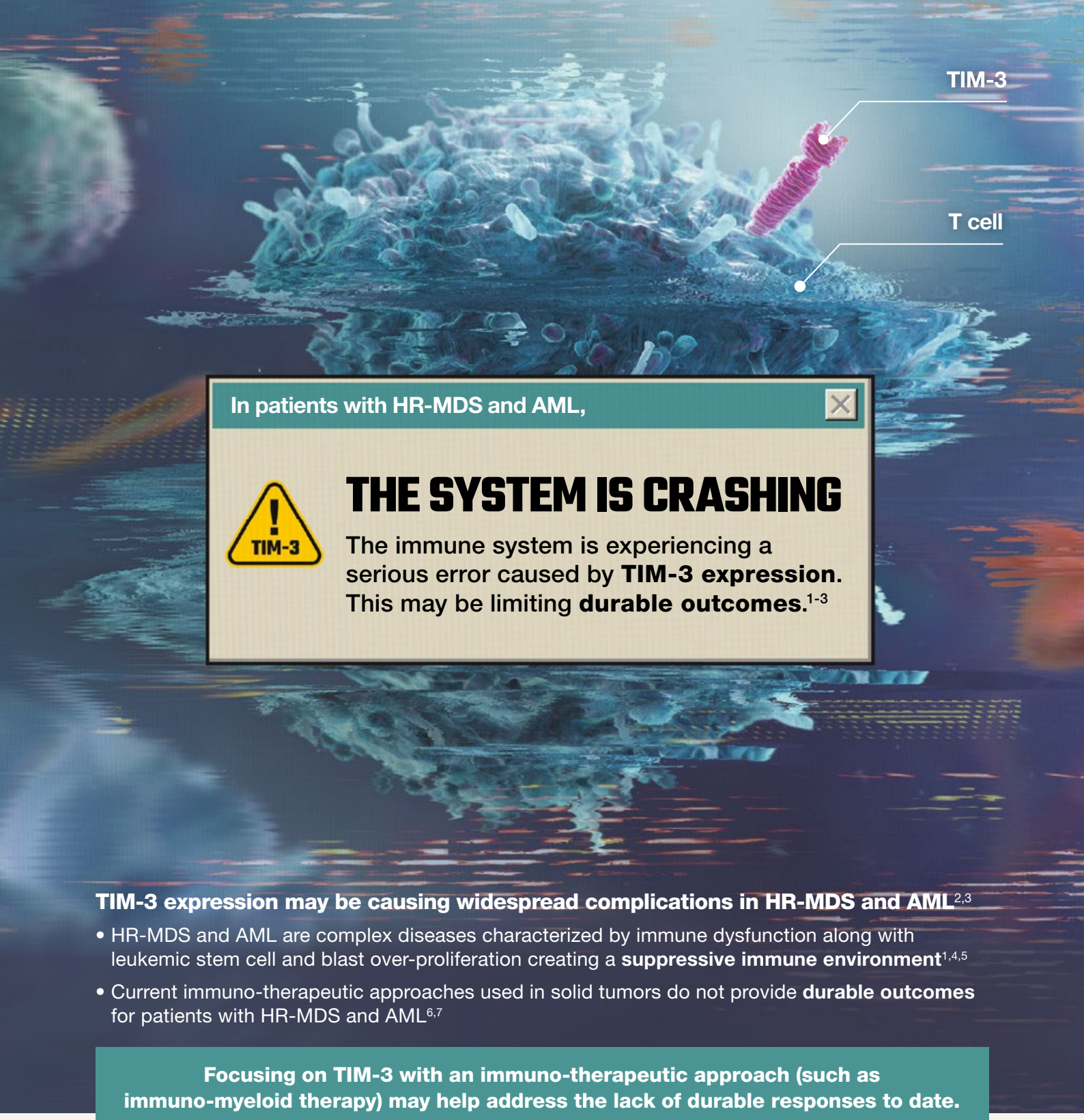
Included in our review of EHA 2021 is a summary of a session on COVID-19 vaccination: 'Antibody Levels in COVID-19 Affected by Age, Gender, and Disease,' alongside a summary of guidelines updates presented at the congress for the management of multiple myeloma. Our congress content also includes summaries of stand-out abstracts, which cover the subjects of COVID-19 in patients with acute leukaemia and analysing haematological formulas to determine iron deficiency anaemia from β-thalassaemia minor.

We had the honour of interviewing Nikhil Munshi, President of the International Myeloma Society (IMS) and Associate Director of the Jerome Lipper Multiple Myeloma Center at the Dana Farber Cancer Institute, Boston, Massachusetts, USA,. He offered valuable insights from his career, current research topics, and the wider field of haematology.

I would like to take this opportunity to thank the Editorial Board, authors, and interviewees for their contributions to providing the latest developments to healthcare professionals.

Spencer Gore

Chief Executive Officer, EMG-Health



TIM-3 expression may be causing widespread complications in HR-MDS and AML[2,3]

- HR-MDS and AML are complex diseases characterized by immune dysfunction along with leukemic stem cell and blast over-proliferation creating a **suppressive immune environment**[1,4,5]
- Current immuno-therapeutic approaches used in solid tumors do not provide **durable outcomes** for patients with HR-MDS and AML[6,7]

Focusing on TIM-3 with an immuno-therapeutic approach (such as immuno-myeloid therapy) may help address the lack of durable responses to date.

LEARN MORE AT TIM3.com

AML, acute myeloid leukemia; HR-MDS, higher-risk myelodysplastic syndrome; TIM-3, T cell immunoglobulin and mucin domain-3.

References: 1. Wang C, Yang Y, Gao S, et al. Immune dysregulation in myelodysplastic syndrome: clinical features, pathogenesis and therapeutic strategies. *Crit Rev Oncol Hematol.* 2018;122:123-132. **2.** Anderson AC, Joller N, Kuchroo VK. Lag-3, Tim-3, and TIGIT: co-inhibitory receptors with specialized functions in immune regulation. *Immunity.* 2016;44(5):989-1004. **3.** Kikushige Y, Shima T, Takayanagi S-I, et al. TIM-3 is a promising target to selectively kill acute myeloid leukemia stem cells. *Cell Stem Cell.* 2010;7(6):708-717. **4.** Chen J, Kao YR, Sun D, et al. Myelodysplastic syndrome progression to acute myeloid leukemia at the stem cell level. *Nat Med.* 2019;25(1):103-110. **5.** Khaldoyanidi S, Nagorsen D, Stein A, et al. Immune biology of acute myeloid leukemia: implications for immunotherapy. *J Clin Oncol.* 2021;39(5):419-433. **6.** Zeidan AM, Knaus HA, Robinson TM, et al. A multi-center phase I trial of ipilimumab in patients with myelodysplastic syndromes following hypomethylating agent failure. *Clin Cancer Res.* 2018. doi:10.1158/1078-0432.CCR-17-3763. **7.** Berger R, Rotem-Yehudar R, Slama G, et al. Phase I safety and pharmacokinetic study of CT-011, a humanized antibody interacting with PD-1, in patients with advanced hematologic malignancies. *Clin Cancer Res.* 2008;14(10):3044-3051.

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Foreword

Dear Colleagues,

It is a great pleasure and honour to introduce this issue of *EMJ Hematology*.

Haematology has always been the discipline that projects medicine into the future, as a precursor for the development of new drugs and new therapeutic techniques. As every year, our European Hematology Association (EHA) congress is an opportunity to present many of these innovations.

In this issue of the journal you will find a review of the impressive progress underway in thalassaemia that is going through a new golden age; two important articles on multiple myeloma are also shared: the first on the management of the elderly patient, which represents an unexpected frontier in recent years, and the second on further brand new drugs that can give a real opportunity to patients who have failed the multiple lines of therapy available today. In this issue you will also find an accurate description of the recurrent episodes of angioedema that may herald myeloproliferative syndromes and a case report on Glanzmann's thrombasthenia.

My choice as Editor-in-Chief for this issue could not fail to go to the review article that analyses the relationship between von Willebrand factor and ADAMTS13 in the syndrome that accompanies SARS-CoV-2 infection. This article is important, not only because it is so dramatically up-to-date, but also because it helps to clarify what was unclear for long months in spring last year. This article discusses the new severe clinical situation in parallel with known haematological conditions, and demonstrates once again that the human body is based on a delicate balance of activations and inhibitions and that breaking this balance often leads to disastrous events. Finally, once again it shows that new pathologies and new clinical situations require time, careful studies, and a multidisciplinary approach to be effectively addressed. What happened last spring was certainly dramatic and we are all still shocked by it, but it must be recognised (despite that today doctors are asked to resolve everything immediately) that an at least partial understanding of the syndrome that follows SARS-CoV-2 infection has been achieved in a very short time: all physicians and scientists involved must be congratulated for this.

Dr Emanuele Angelucci

Chair, Hematology and Transplant Unit, Ospedale Policlinico San Martino; Transplant Program Director, Istituto di Ricovero e Cura a Carattere Scientifico (IRCCS), Genova, Italy.

A BREAKTHROUGH
IN CHEMOTHERAPY IN HIGH-RISK* AML[1]

www.vyxeos.eu

* High-risk AML defined as newly diagnosed t-AML or AML-MRC
† Superior overall survival vs conventional chemotherapy in patients with high-risk* AML[2]
‡ Estimated from Kaplan Meier curve

TOGETHER. LONGER.†

Superior overall survival vs conventional chemotherapy in patients with high-risk* AML[2]

AML 5-YEAR DATA

OS benefit sustained over five years:
18% with Vyxeos Liposomal vs 8% with conventional chemotherapy, HR: 0.70, 95% CI: 0.55-0.91‡[3]

OS maintained above 50% at five years
in a post-hoc analysis of Vyxeos Liposomal patients who underwent transplant‡[3]

Comparable frequency and severity of adverse events between Vyxeos Liposomal and conventional chemotherapy[2]

For more meaningful time together

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LAYING THE FOUNDATION
TOWARDS LONG-TERM SURVIVAL IN HIGH-RISK* AML

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Please refer to the Summary of Product Characteristics before prescribing.
Presentation: Purple lyophilised cake of powder for concentrate for solution for infusion. Each vial contains 44 mg of daunorubicin and 100 mg of cytarabine. After reconstitution the solution contains 2.2 mg/mL daunorubicin and 5 mg/mL cytarabine encapsulated in liposomes in a fixed combination in a 1:5 molar ratio. **Indication:** For the treatment of adults with newly diagnosed, therapy-related acute myeloid leukaemia (t-AML) or AML with myelodysplasia-related changes (AML-MRC). **Dosage and administration:** For intravenous infusion use only. An in-line membrane filter may be used provided the minimum pore diameter of the filter is greater than or equal to 15 µm. It must not be administered via an intramuscular, intrathecal, or subcutaneous route. Refer to the full SmPC for detailed information on preparation of solution for infusion. Treatment should be initiated and monitored under the supervision of a physician experienced in the use of chemotherapeutic medicinal products. Recommended dosing schedule for induction of remission: 44 mg/100 mg/m^2, administered intravenously over 90 minutes on days 1, 3, and 5 as the first course of induction therapy; then on days 1 and 3 as subsequent course of induction therapy, if needed. Recommended dosing schedule for consolidation: The first consolidation cycle should be administered 5 to 8 weeks after the start of the last induction. The recommended dosing schedule is 29 mg/65 mg/m^2, administered intravenously over 90 minutes on days 1 and 3 as subsequent courses of consolidation therapy, if needed. Dose adjustments during treatment may be required in hypersensitivity symptoms and cardiotoxicity. Assessment of cardiac function prior to start of treatment is recommended. Renal impairment: Dose adjustment is not required for patients with mild (creatinine clearance [CrCL] 60 mL/min to 89 mL/min by Cockcroft Gault equation [C-G]) or moderate (CrCL 30 mL/min to 59 mL/min) renal impairment. There is no experience in patients with severe renal impairment (CrCL 15 mL/min to 29 mL/min) or end-stage renal disease. It should only be used in patients with severe renal impairment if the benefits outweigh the risks. Hepatic impairment: Dose adjustment is not required for patients with a bilirubin level less than or equal to 50 µmol/L. There is no experience in patients with hepatic impairment resulting in a bilirubin level greater than 50 µmol/L. It should only be used in patients with severe hepatic impairment if the benefits outweigh the risks. Elderly population (≥65 years): No dose adjustment is required. Paediatric population: The safety and efficacy in children aged 0–18 years has not yet been established. **Contraindications:** Hypersensitivity to the active substance or to any of the excipients. **Warnings, precautions and interactions:** Do not substitute or interchange with other daunorubicin and/or cytarabine-containing products. Severe myelosuppression and serious or fatal haemorrhagic events have been reported. Due to the long plasma half-life of Vyxeos Liposomal, time to recovery of ANC and platelets may be prolonged and require additional monitoring. Prophylactic anti-infectives may be administered during the period of profound neutropenia until ANC returns to 500/µL or greater. If myelosuppressive complications occur, appropriate supportive measures should be used. Blood counts should be regularly monitored until recovery. As cardiotoxicity is a known risk prior therapy with anthracyclines, pre-existing cardiac disease, previous radiotherapy of the mediastinum, or concomitant use of cardiotoxic products may increase the risk. Hepatotoxic medicinal products may impair liver function and increase toxicity. Evaluation of hepatic and renal function is recommended prior to administration and periodically during treatment. Blood uric acid levels should be monitored and appropriate therapy initiated if hyperuricemia develops. Each vial of Vyxeos Liposomal contains 100 mg of copper gluconate. It should only be used in patients with a history of Wilson's disease or other copper-related disorder if the benefits outweigh the risks. To avoid local tissue necrosis care should be taken to ensure that there is no extravasation of Vyxeos Liposomal during administration. Administration of live or live-attenuated vaccines should be avoided. Killed or inactivated vaccines may be administered; however, the response to such vaccines may be diminished. The absorption of oral accompanying medicinal products may be considerably influenced by gastrointestinal mucositis and/or diarrhoea frequently occurring in association with intensive chemotherapy. **Pregnancy, lactation and fertility:** There are no data on use in pregnant women. It should not be used during pregnancy unless the benefit of treatment outweighs the risk. It is not known if Vyxeos Liposomal is excreted in human milk therefore mothers should be advised to discontinue breastfeeding during therapy. Patients should be advised to avoid becoming pregnant while receiving Vyxeos Liposomal. Male patients and women of childbearing potential must use an effective method of contraception during treatment and for 6 months following the last dose. Male fertility may be compromised by treatment. **Undesirable effects: Please refer to the full SmPC for the complete list of undesirable effects.** The most frequently occurring adverse reactions were hypersensitivity, febrile neutropenia, oedema, diarrhoea/colitis, mucositis, fatigue, musculoskeletal pain, abdominal pain, decreased appetite, cough, headache, chills, arrhythmia, pyrexia, sleep disorders, and hypotension. The most serious and frequently occurring ADRs were infection, cardiotoxicity and haemorrhage. **Overdose:** There is no specific antidote for overdose and treatment should be symptomatic. **Storage and Handling:** Store in a refrigerator (2°C - 8°C). Shelf life of unopened vials: 2 years. Keep vial in the original carton to protect from light and store in an upright position. Vyxeos Liposomal is a cytotoxic medicinal product intended for single use only. Any unused medicinal product or waste material should be disposed of in accordance with local requirements for cytotoxic agents. **Legal category:** POM. **Marketing authorisation number:** EU/1/18/1308/001. **Package quantity and Cost:** carton containing 1 × 50 mL vial. Price differs across countries. Further information is available from the **Marketing Authorisation Holder:** Jazz Pharmaceuticals Ireland Ltd., 5th Floor, Waterloo Exchange, Waterloo Road, Dublin D04 E5W7, Ireland.

Date of preparation: November 2019. **Job Code:** INT-VYX-1900009
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For country specific information please refer to your local SmPC or Product Monograph

Adverse events should be reported. Healthcare professionals are asked to report any suspected adverse events via their national reporting system. In the United Kingdom reporting forms and information can be found at: **https://yellowcard.mhra.gov.uk/** Adverse events should also be reported to Jazz Pharmaceuticals by email to **aereporting@jazzpharma.com** or by fax to +44 (0) 1865 598765

References:
1. U.S. Food and drug administration 2017. FDA news release: FDA approves first treatment for certain types of poor-prognosis acute myeloid leukemia.
2. Lancet JE *et al.* J Clin Oncol 2018; 36(26): 2684-92.
3. Lancet JE *et al.* Presented at the Congress of the European Hematological Association (EHA) 2020, EP556.

Abbreviations:
AML: acute myeloid leukaemia. **AML-MRC:** AML with myelodysplasia-related changes. **CI:** confidence interval. **Conventional chemotherapy:** 7+3 in induction and 5+2 in second induction and consolidation when given. **HR:** hazard ratio. **OS:** overall survival. **t-AML:** therapy-related AML.

Date of preparation: June 2021 **Job code:** INT-VYX-2100082

Congress Review

Review of the European Hematology Association (EHA) 2021 Virtual Congress

Location: EHA 2021

Date: 9th–17th June 2021

Citation: EMJ Hematol. 2021;9[1]:12-24. Congress Review.

THE GLOBAL community of clinicians and researchers shared in the latest advances in haematology care online at the 26th European Hematology Association (EHA) 2021 Virtual Congress. Despite the ongoing impact of the COVID-19 pandemic, affecting the ability for this large network of engaged healthcare practitioners to meet together to advance their individual and collective understanding of haematological care, the virtual congress provided a fantastic opportunity for the usual shared education and discussion to continue undaunted.

In his opening ceremony address, John Gribben, President of EHA, outlined the value and intention of the congress: "the congress and all its components are interwoven with the latest research and clinical practice updates, as well as various opportunities to connect with your colleagues from all around the world." In addressing the response to the challenges of the past year, Gribben highlighted a proverb: 'If you want to go quickly, go alone. If you want to go far, go together.' This ethos of shared journeying was evident throughout the congress, as sessions were shared amongst experts from around the globe; contributed to by EHA and partner associations; and carried by the many voices of expert clinicians, early-career researchers, laboratory and scientific researchers, and patient advocates.

The 9-day congress included 4 core, cross-discipline days followed by 5 thematic days, sharing plenary sessions, symposia, abstract presentations, and debates to cover the full discipline of haematology from the laboratory to the clinic, including leukaemias and lymphomas, red and white cell disorders, haemoglobinopathies, and transfusion medicine. EHA guideline sessions shared summary updates for practising clinicians, including joint sessions with the European Society for Medical Oncology (ESMO) and other partner associations for detailed and practical education.

More than 1,800 abstracts were submitted to EHA 2021 to share insights across the

"...the virtual congress provided a fantastic opportunity for the usual shared education and discussion to continue undaunted."

sub-disciplines of haematology. The authors of several standout abstracts from the congress have provided summaries of their research, shared in this issue of *EMJ Hematology*. These include the clinical experience at a haematological centre of patients with COVID-19 and acute leukaemia, as well as an analysis comparing the value of different formulas to discern iron deficiency anaemia from β-thalassaemia minor.

Stand-out highlights from the congress, sharing hot-topic research news, are summarised in our following congress review. These include a French national registry analysis of the efficacy of chimeric antigen receptor T cell therapy in diffuse large B-cell lymphoma, the results of treatment efficacy studies in multiple myeloma, and genetic insights in juvenile haemochromatosis, among others. EHA 2021 highlighted the findings from these studies as of highest impact for current and upcoming practice in haematology, and summaries of these findings are shared to allow *EMJ Hematology* to continue the conversation from EHA 2021. We also interviewed EHA 2021 Chair of Scientific Program Committee Ruud Delwel, who gave the opening address for the congress; he outlined for us how his goals for EHA 2021 shaped the delivery of the congress.

While many expert and valued haematologists were celebrated at the congress, highlighting their research work or sharing their career insights, three major awards were presented as part of EHA 2021. The David Grimwade Award was presented to Olivier Bernard to recognise his role as a leading and active basic and translational researcher, particularly for his work in delineating the role of JAK2 and TET2 in oncogenesis and their impact on haematopoiesis. The José Carreras Award winner for 2021 was Elias Campo, recognising his contributions to haematologic translational and clinical research as a clinical pathologist pioneering genetic understanding in modern haematological practice. Finally, the prestigious Jean Bernard Lifetime Achievement Award honoured the work of Christine Chomienne for her 25-year career in clinical haematology, translational research, and active impact in EHA including in her term as EHA President 2013–2015.

While the hope this year had been to walk the Ringstrasse in Vienna, Austria, alongside haematology colleagues, the virtual format did not diminish the fantastic delivery and atmosphere of this key event in haematology care. Read on for our key scientific insights from EHA 2021, and we look forward to sharing in this community again, hopefully in-person, in Vienna in 2022. ■

"...the virtual format did not diminish the fantastic delivery and atmosphere of this key event in haematology care."

EHA 2021 REVIEWED →

Efficacy of CAR T Therapy in Patients with Diffuse Large B-Cell Lymphoma

DESCAR-T is the French national registry for patients treated with commercial chimeric antigen receptor (CAR) T cells across all haematological malignancies, with the goal to collect real-world data, including safety and effectiveness, up to 15 years after CAR T cell infusion. In a new study, a team led by Steven Le Gouill, Assistant Professor in Clinical Hematology, Nantes University Hospital, France, sought to investigate CAR T efficacy in patients with diffuse large B-cell lymphoma (DLBCL) who were registered in the DESCAR-T database. The results of this study were presented as part of an oral session at EHA 2021.

Phase II clinical trials have demonstrated that CAR T cells can provide long-term disease control in relapsed/refractory patients with B-cell acute lymphoblastic leukaemia or DLBCL. The French Health Authority (HAS) commissioned specific real-world data on this; they stated the data had to be characteristic of the CAR-T-eligible population in the 'intention-to-treat' category, have long-term follow-up of 15 years, and include previous therapy description. To fulfil this need for a national registry, DESCAR-T was created in 2019.

The DESCAR-T database saw approximately 50 new patients registered each month, indicating the success of CAR T therapy for patients. Of the patients in the database, CAR T cells were ordered for 607 patients and 550 had been infused. The median time from CAR T order to infusion was 50 days. Of the patients who completed CAR T therapy, 350 patients were infused with axicabtagene and 200 received tisagenlecleucel. Patient characteristics and clinical outcomes of 537 patients with DLBCL who were registered in the DESCAR-T database were measured in this study. In an analysis of the response data from 460 infused patients, the authors found that 40% achieved complete remission and 30% achieved partial remission by Day 30. The progression-free survival at 6 months calculated from the time of CAR-T infusion was 44.5% (39.6–49.2) months.

"The DESCAR-T registry confirmed the clinical trial efficacy of CAR T therapy in the real world."

The authors concluded the analysis by stating that the DESCAR-T registry confirmed the clinical trial efficacy of CAR T therapy in the real world. ■

Humoral Response of COVID-19 Vaccine in Haematopoietic Cell Transplantation and CAR-T Therapy

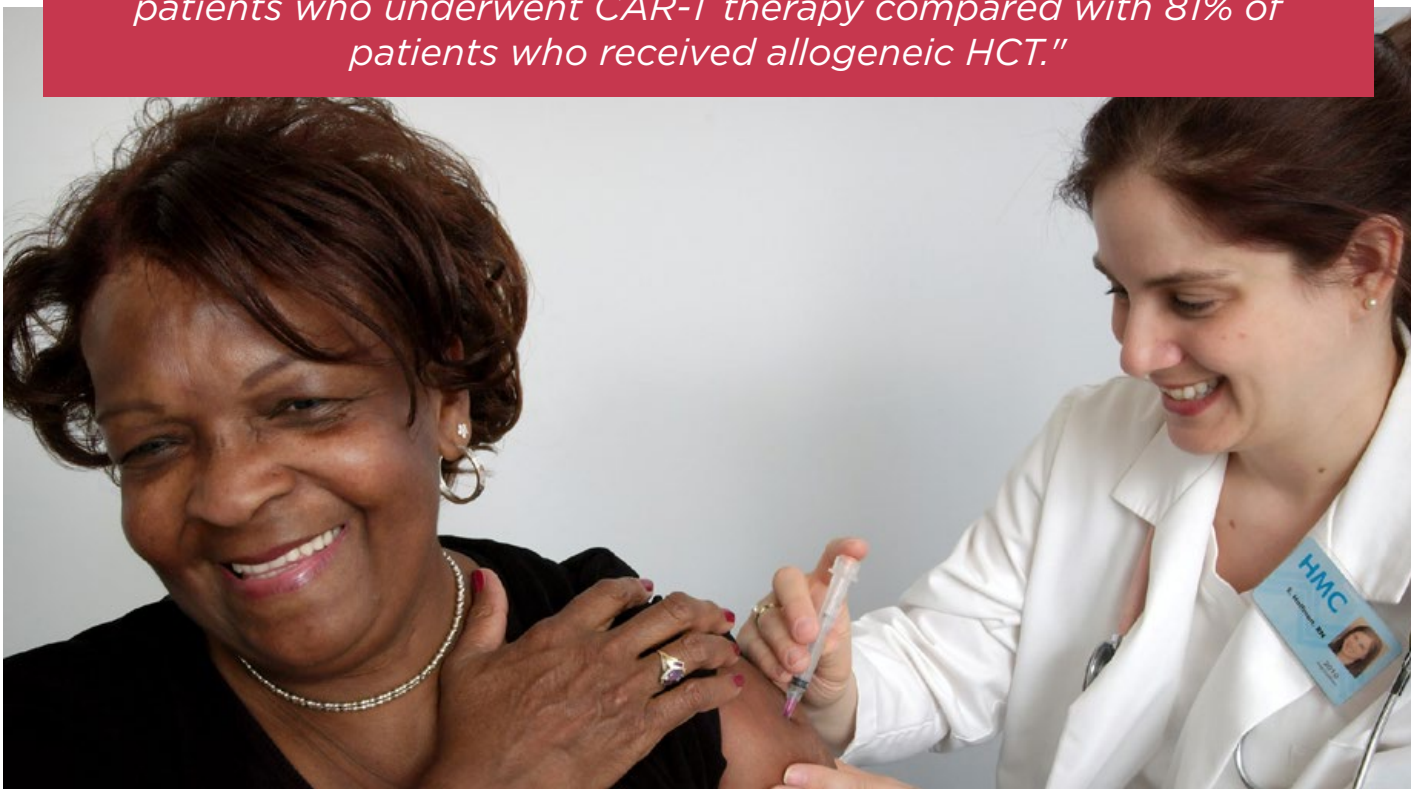
COVID-19 has been linked to the occurrence of other severe disease and increased mortality rates in patients who have undergone hematopoietic cell transplantation (HCT). The approved Pfizer/BioNTech BNT162b2 vaccine has proven to be necessary for the prevention of severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) infection, especially in patients with health conditions associated with immunosuppression. Despite the benefits of the BNT162b2 vaccine, the efficacy and safety of this vaccine in patients undergoing immunologic cell therapy has not been effectively recorded. A new study presented on 12th June 2021 during EHA 2021 assessed BNT162b2 vaccine immunogenicity and safety in patients who underwent HCT and chimeric antigen receptor therapy (CAR-T).

The study, presented by Ron Ram, BMT Unit, Tel Aviv Sourasky Medical Center, Israel, observed the humoral immune response of 79 patients who had recently been vaccinated with BNT162b2 at the medical centre. There were 66 patients in the HCT group and 14 patients in the CAR-T therapy group. All participants were vaccinated according to the European Society for Blood and Marrow Transplantation (EBMT) guidelines. Generally, the vaccine was effective and any adverse effects resolved, apart from one graft rejection that is currently under examination.

Humoral antibody response was observed in only 36% of patients who underwent CAR-T therapy compared with 81% of patients who received allogeneic HCT. Patients diagnosed with B cell aplasia as well as those who received the vaccine shortly after CAR-T therapy were less likely to develop antibodies.

In conclusion, the results demonstrated that the humoral response to the BNT162b2 vaccine displayed a good response in patients who had undergone allogeneic HCT but diminished in those patients receiving CAR-T. ■

"Humoral antibody response was observed in only 36% of patients who underwent CAR-T therapy compared with 81% of patients who received allogeneic HCT."



Improved Progression-Free Survival Shown in Myeloma by Adding Daratumumab to Treatment

THE FRONT-RUNNER of novel treatments for newly diagnosed multiple myelomas (NDMM) is a modern initiative that incorporates daratumumab. This addition to bortezomib, thalidomide, and dexamethasone (D-VTd) induction/consolidation was compared with velcade, thalidomide, and dexamethasone (VTd) alone in a French study. D-VTd demonstrated superior efficacy in combination with autologous stem cell transplantation (ASCT) by producing longer progression-free survival (PFS) rates, most beneficial in patients who had previously received VTd induction/consolidation.

This two-part study led by Philippe Moreau, spanning 2 years, revealed significantly improved post-ASCT outcomes in patients with NDMM and lays strong foundations for the development of further maintenance strategies in this field. Labelled the CASSIOPEIA trial, the current Phase III study included 1,085 participants with transplant-eligible NDMM in its first stage, with a randomised, open-label, active-controlled, parallel-group design. In this step, D-VTd induction/consolidation demonstrated superior depth of response, better minimal residual disease negativity scores, and prolonged PFS in comparison with VTd.

The second section of the study was an interim analysis comparing D-VTd and VTd treatments using observation treatment, conducted in 886 responders progressing from the previous stage of investigation. This brought forward evidence that patients maintained longer PFS in the daratumumab arm; however, stratification showed that this benefit was exclusive to patients previously treated with VTd in the first stage of the trial.

The researchers acknowledge that further longitudinal study is required to assess the potential the findings bring for overall survival and long-term PFS2. The evidence is promising for patients with myeloma and there is no doubt that ongoing studies, such as GRIFFIN, PERSEUS, and AURRIGA, will build on the strategies investigated to bring us closer to an optimal maintenance strategy; the next steps are expected to combine daratumumab with lenalidomide. ■

"D-VTd demonstrated superior efficacy in combination with autologous stem cell transplantation (ASCT) by producing longer progression-free survival (PFS) rates, most beneficial in patients who had previously received VTd induction/consolidation."

Addition of Daratumumab Improved Overall Survival in Multiple Myeloma

MULTIPLE Myeloma (MM) is a life-threatening bone marrow cancer that is more prevalent in elderly patients. Those diagnosed have a shorter life expectancy by approximately ten years. Individuals who are not diagnosed early have a much poorer prognosis of only six months. Therefore, there is great interest in exploring novel therapeutics to increase overall survival of patients.

A Phase III multicentre study that took place from March 2015 to January 2017 evaluated the difference in efficacy between the immunomodulatory drugs lenalidomide and dexamethasone (Rd) versus Rd plus daratumumab (D-Rd). Researchers recruited 737 eligible patients who could not have high-dose chemotherapy or were transplant-ineligible. Patients were given either Rd or D-Rd in a randomised 1:1 ratio in cycles of 28 days. The doses of Rd were the same in both groups (R: 25 mg; d: 40 mg); patients receiving D-Rd were given an additional 16 mg of daratumumab. The results showed that in patients receiving D-Rd there was a 44% decrease in the risk of disease progression and death after treatment compared with Rd alone. Further to this, 32% of patients in the D-Rd group had a significant reduction in risk of death compared to the Rd group.

"D-Rd significantly improved overall survival and response rate (93% versus 82%) compared to Rd alone."

5-year overall survival was higher in the D-Rd group (66.3%) in comparison to the Rd group (53.1%). Interestingly, the overall survival rate was maintained, with a 47% reduction in disease progression or death (hazard ratio: 0.53; 95% confidence interval: 0.43–0.66; p<0.0001). Adverse events reported were similar in both groups and there were no new safety concerns.

The researchers concluded that there was greater treatment efficacy when daratumumab was added to Rd. The promising data showed that D-Rd significantly improved overall survival and response rate (93% versus 82%) compared to Rd alone. The next steps could involve considering how to achieve the same desirable outcomes with fewer moderate-severe adverse events. Nonetheless, this research allows us to be optimistic for future treatment for patients with MM. ■

Terbutaline and Restoration of T Helper Cell Dysregulation in Immune Thrombocytopenia

IMMUNE thrombocytopenia is an autoimmune pathology characterised by a low platelet count. Dysregulation of T helper (Th) cells, specifically the Th1 and Th17 subsets, plays a central role and is associated with the production of autoantibodies against platelets. Recent studies showed that the β2-adrenergic receptor (β2-AR) is the primary adrenergic receptor on immune cells. Furthermore, the nervous system was found to directly modulate Th cell polarisation. For this reason, Xiao-Hui Zhang, Peking University People's Hospital, Beijing, China, and collaborators explored the regulation of the sympathetic nervous system on Th cell polarisation and the role of β2-AR signalling in immune cell development and pathways during immune thrombocytopenia. The results of this study were presented during the Presidential Symposium at this year's EHA 2021, 9th–17th June 2021.

Using 6-hydroxydopamine, the researchers chemically depleted the sympathetic nerves in an active immune thrombocytopenia mouse model. Sympathectomised mice displayed a significantly longer platelet recovery time, lower survival, and expressed more Th1 genes compared with non-sympathectomised mice. Subsequent injection of terbutaline, a β2-AR agonist, stimulated β2-AR signalling and improved platelet counts in both groups of mice. Moreover, terbutaline also restored the immune imbalance of Th cells to control levels.

Finally, peripheral blood mononuclear cells, isolated from people with immune thrombocytopenia, were treated with terbutaline. Treatment of these cells with the β2-AR agonist had no effect on the proliferation of $CD4^+$ or $CD8^+$ T cells. Notably, stimulation of these cells with terbutaline inhibited the differentiation of Th1 cells while promoting the differentiation of Th2 and regulatory T cells.

In conclusion, impaired sympathetic innervation and Th dysregulation is crucial for driving the pathogenesis of immune thrombocytopenia. However, this can be reversed by terbutaline administration, which potentially represents a novel therapeutic approach for the treatment of this blood disorder. ■

"[Th dysregulation] can be reversed by terbutaline administration, which potentially represents a novel therapeutic approach."

Pegcetacoplan Shows Sustainable Promise in Paroxysmal Nocturnal Haemoglobinuria

A PHASE III study spanning 48 weeks has demonstrated favourable results for pegcetacoplan as a therapeutic option for treating paroxysmal nocturnal haemoglobinuria (PNH). This haematopoietic stem cell disorder has previously been combatted using eculizumab, which was found to produce lower haemoglobin (Hb) levels in a randomised controlled study compared to pegcetacoplan. The findings of the study from the University of Paris, France, were shared at EHA 2021 and in a press release from the congress dated 12th June 2021.

Split into two branches of treatment, the study included adults with PNH and haemoglobin <10.5 g/dL after stable treatment with eculizumab for 3 months. A 4-week run-in period was followed by 16 weeks of monotherapy, randomised to either pegcetacoplan (41 participants) or eculizumab (39 participants). A further 32 weeks of open-label pegcetacoplan treatment was then prescribed for all participants, and notably patients switching at this stage displayed improved Hb levels at Week 48. Clinical parameters also improved in this switched group, with 75% remaining free from transfusion, comparable to the unswitched pegcetacoplan arm.

Overall, patients with a suboptimal response to eculizumab experienced a durable improvement when switched to pegcetacoplan. However, It should be mentioned that 6% of participants experienced adverse events possibly related to pegcetacoplan and 15% discontinued treatment as a result of this. Further study will focus on methods to reduce these treatment-emergent adverse events.

The study findings are positive for prevention of anaemia in PNH, especially as 72% of eculizumab-treated patients currently experience chronic anaemia and 36% require at least one blood transfusion per year. Following these positive findings, more countries may follow in the footsteps of the USA in approving pegcetacoplan for the treatment of PNH in adults. ■

"The study findings are positive for the future prevention of anaemia in PNH, especially as 72% of eculizumab-treated patients currently experience chronic anaemia."

Juvenile Haemochromatosis Caused by Mutations in the *PIGA* Gene

HEREDITARY haemochromatosis, a condition characterised by enhanced gastrointestinal iron absorption, is the most common genetic disorder among the Caucasian population. If untreated, excess iron deposition causes multiple organ dysfunction in ageing patients. In addition to the late-onset adult form of haemochromatosis, rare subtypes have been described with severe iron overload in children. Oriana Marques, Department of Pediatric Oncology, Hematology, Immunology and Pulmonology, Heidelberg University, Germany, and colleagues have found a novel subtype of juvenile haemochromatosis resulting from mutations in the *phosphatidylinositol glycan class A* (*PIGA*) gene, which encodes a protein involved in the biosynthesis of glycosylphosphatidylinositol (GPI) lipid anchors. The research findings were shared during the Presidential Symposium at EHA 2021, 9th–17th June 2021.

Initially, three juvenile patients with neurological deficits were diagnosed with systemic iron overload and *PIGA* mutations. To further investigate the pathomechanism associated with iron accumulation, the researchers applied CRISPR/Cas-mediated gene deletion of *PIGA* in a liver cell line. *PIGA* deletion was found to prevent cell membrane attachment of haemojuvelin, which facilitates the formation of an active bone morphogenetic receptor complex that signals to increase hepcidin, the key regulator of systemic iron homeostasis. Therefore, a lack of *PIGA* reduces hepcidin levels and ultimately causes the body to store excess iron. Moreover, ceruloplasmin, a ferroxidase involved in cellular iron export, is also GPI-anchored. Consequently, *PIGA* depletion will substantially decrease ceruloplasmin to enhance intracellular iron accumulation and exacerbate the iron overload.

"These results identify not only a novel form of juvenile hereditary haemochromatosis but also its underlying molecular mechanism."

These results identify not only a novel form of juvenile hereditary haemochromatosis but also its underlying molecular mechanism. The function of two GPI-anchored proteins, haemojuvelin and ceruloplasmin, involved in maintaining iron homeostasis, is impaired in patients with germline *PIGA* mutations. Identifying these mutations may allow for clinical assessment of potential and future iron overload in affected individuals. ■

Comparison of Zanubrutinib to Ibrutinib Uncovers Improved Treatment Profile

HARNESSED to treat chronic lymphocytic leukaemia (CLL) and small lymphocytic lymphoma (SLL), zanubrutinib has demonstrated a more selective inhibition of bruton tyrosine kinase (BTK) to achieve improved safety and efficacy, compared to ibrutinib. At EHA 2021, Peter Hillmen, St James's University Hospital, Leeds, UK, shared the findings of a Phase III randomised controlled trial, the ALPINE study, in a press release dated 11th June 2021, revealing that zanubrutinib significantly outperformed ibrutinib with relation to response rates, survival rates, and safety outcomes.

For a cohort of 415 patients with CLL/SLL, with inclusion criteria including lymphadenopathy on CT or MRI, analysis at 12 months highlighted an overall response rate of 78% with zanubrutinib but only 63% with ibrutinib. Intervention groups received either 160 mg zanubrutinib twice daily or 420 mg ibrutinib once daily. Concerning safety, zanubrutinib performed better than ibrutinib in terms of episodes of atrial fibrillation, major bleeding, and adverse events leading to discontinuation, as well as demonstrated a more selective and efficacious inhibition of BTK.

The only areas in which ibrutinib remained superior were with the ease of taking one dose per day and the rate of neutropenia (zanubrutinib: 28%; versus ibrutinib: 22%). Improved response rates, progression-free survival, and lower rates of atrial flutter support that zanubrutinib offers a superior treatment to patients with CLL and SLL.

These findings present an exciting development in the ongoing challenge of addressing B cell malignancies. While inbrutinib is currently considered first-in-class for CLL/SLL and is approved for use in >80 countries, these data prompt future consideration for the role of zanubrutinib in further research and clinical practice. ■

"...zanubrutinib significantly outperformed ibrutinib with relation to response rates, survival rates, and safety outcomes."

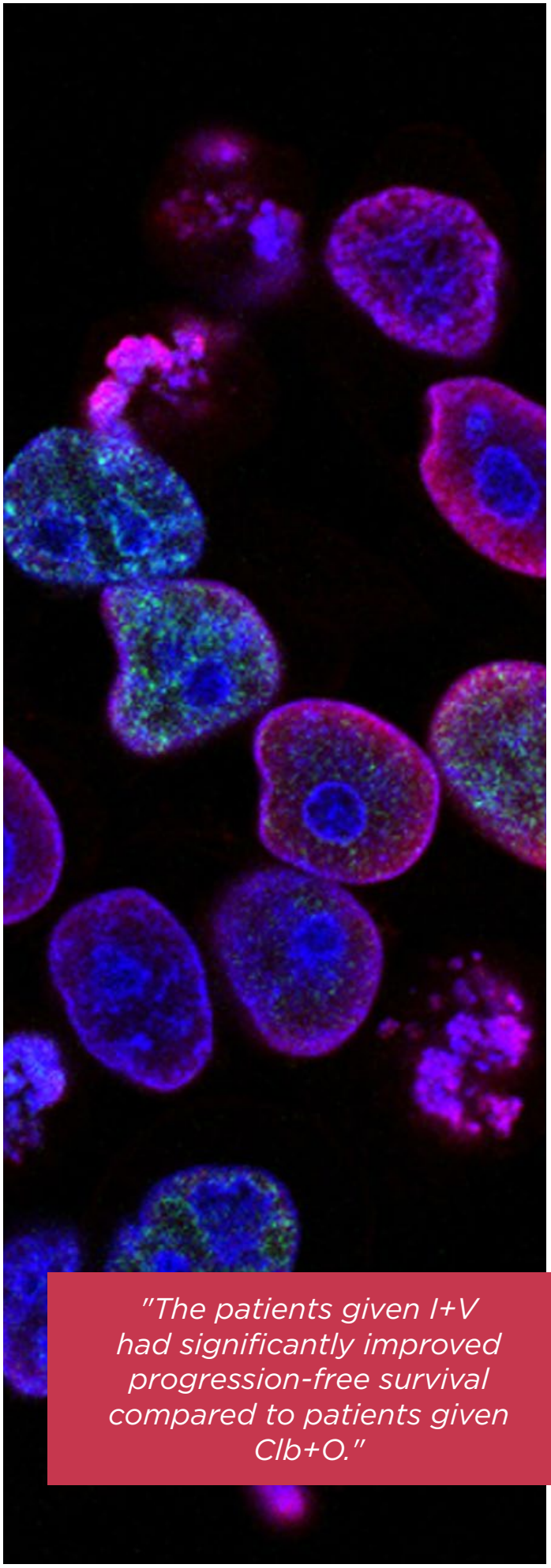
Improved Overall Survival in Patients Taking Ibrutinib and Venetoclax

CHRONIC lymphocytic leukaemia (CLL) is a serious cancer that causes the over-production of white blood cells, namely lymphocytes. This cancer predominately affects middle-aged and elderly patients. Symptoms include fatigue, shortness of breath, and repeated infections. CLL has a poor prognosis: 2–3 years life expectancy after diagnosis. Therefore, there is an urgent need to improve therapeutics and progression-free survival.

Arnon Kater, Amsterdam Medical Center, University of Amsterdam, the Netherlands, shared the findings of a recent clinical trial at EHA 2021 in a press release dated 12th June 2021. The study evaluated the combination of ibrutinib and venetoclax (I+V) compared with combined chlorambucil and obinutuzumab (Clb+O). Researchers predicted the former combination would produce promising results due to their complementary mechanisms: ibrutinib prevents the mobility of CLL cells and venetoclax then destroys the immobilised circulating cancer cells.

Researchers recruited 211 eligible patients who were then either treated with I+V or Clb+O in a randomised 1:1 ratio with a 27.7 month follow-up. The patients given I+V had significantly improved progression-free survival compared to patients given Clb+O. Further to this, the study found the rate of undetectable minimal residual disease in bone marrow and blood examination was significantly higher in patients receiving I+V, which could suggest that there are fewer circulating cancer cells in I+V patients. Furthermore, 84.5% of I+V patients went on to maintain this low rate of minimal residual disease.

These results suggest that a careful combination of inhibitors could improve prognosis and overall survival in CLL. Future research with a larger sample size could reinforce these results, and may evaluate other combinations of inhibitors that may be equally effective with fewer adverse events. ■



"The patients given I+V had significantly improved progression-free survival compared to patients given Clb+O."

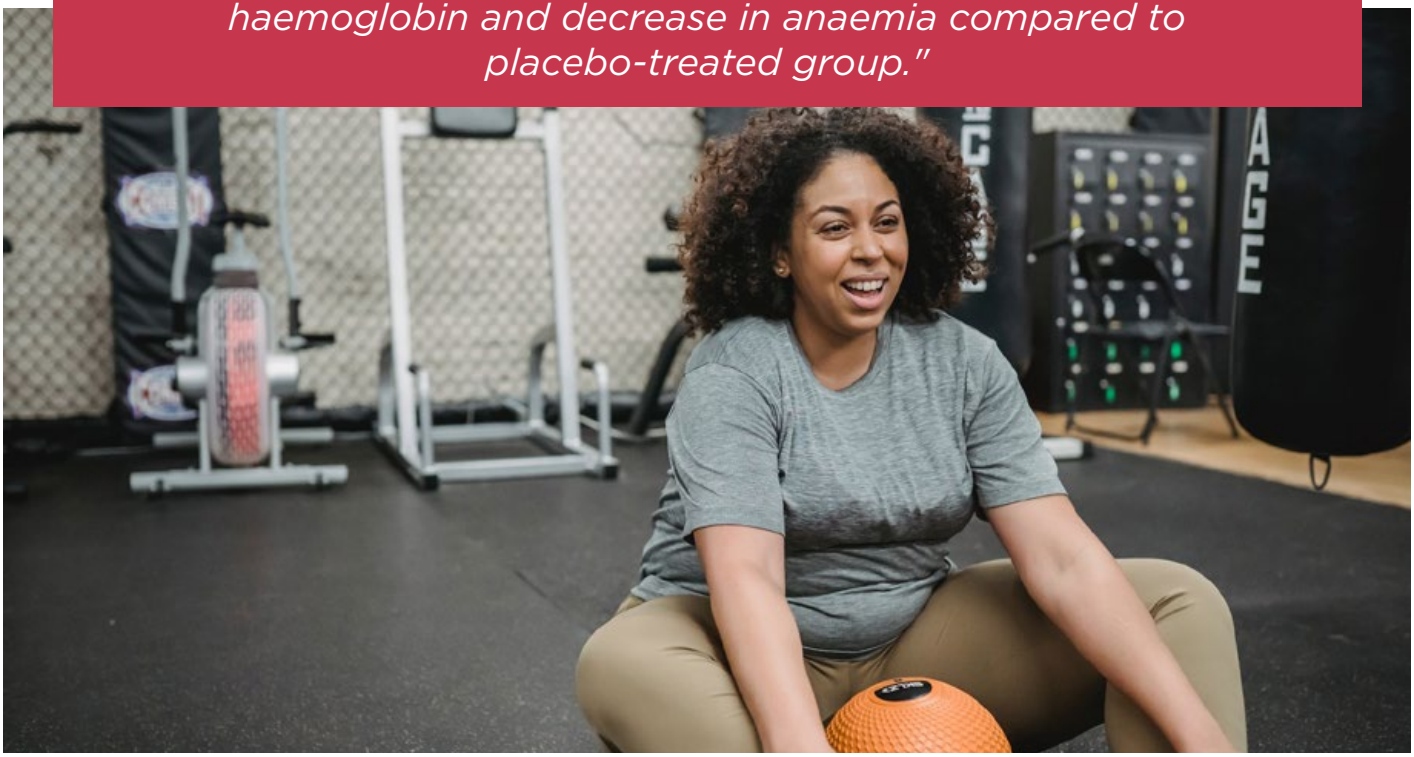
Luspatercept for Anaemia in Non-transfusion-dependent β-Thalassaemia

COMPROMISED production of haemoglobin results from an inherited blood disorder in non-transfusion-dependent (NDT) β-thalassaemia. This disorder presents with mild–moderate chronic anaemia and iron overload, which could lead to the development of serious morbidities in several organs and reduced quality of life, regardless of transfusion-dependence. Currently, there are no therapies approved for the treatment of anaemia in NTD β-thalassaemia. However, a new study suggests luspatercept, an approved treatment of anaemia in transfusion-dependent β-thalassaemia, could be useful for patients diagnosed with NTD β-thalassaemia. The results of the BEYOND study, a randomised, double-blind, placebo-controlled Phase II study that enrolled 145 patients diagnosed with NTD β-thalassaemia, was presented by Ali Taher, American University of Beirut Medical Center, Lebanon, at the EHA 2021 congress.

The aim of the study was to compare the effectiveness and safety of luspatercept with placebo in the treatment of NTD β-thalassaemia. All participants received supportive care and were followed to 24 weeks after treatment. Participants treated with luspatercept showed significant improvement, with an increase in the production of haemoglobin and decrease in anaemia compared to the placebo-treated group. Additionally, approximately 90% of the patients treated with luspatercept did not require transfusion throughout the 24-week study. Alongside an increase in haemoglobin in the luspatercept-treated group, it was noted that quality of life improved, with reduced clinical symptoms associated with anaemia such as fatigue and weakness.

The occurrence of adverse events caused by the treatment were comparable between the luspatercept and placebo groups, and there were no thromboembolic or thrombophlebitis incidents during the trial. Overall, luspatercept was found to be safe and effective over the 24-week study and demonstrated significant improvements for anaemia and anaemia-associated symptoms in NTD β-thalassaemia. ■

"Participants treated with luspatercept showed significant improvement, with an increase in the production of haemoglobin and decrease in anaemia compared to placebo-treated group."



Congress Interview

Ruud Delwel

Department of Hematology, Erasmus MC Cancer Institute, Rotterdam, the Netherlands; Chair of Scientific Program Committee, European Hematology Association (EHA) 2021 Virtual Congress

RUUD Delwel, Chair of Scientific Program Committee, European Hematology Association (EHA) 2021 Virtual Congress, spoke with EMJ ahead of the congress about his role within the society, research interests and recent publications, and his thoughts on the challenges and innovations in haematology research.

Q1 With over 30 years studying and working in this field, why haematology? What drew you to this discipline and what motivates you to continue pursuing this career path?

When I finished my biology study, with a major focus on molecular and cellular biology, I had to decide what my next step would be. I remember reading a newspaper article about a doctor who was based at the Erasmus MC Cancer Institute, Rotterdam, the Netherlands, and performed bone marrow transplantation in patients with leukaemia. Since this was a procedure which fascinated me, I decided to make contact with the specialist in question. It transpired he was Professor Löwenberg, one of the founding members of EHA. I can still vividly recall that phone conversation. A day later, I had a job.

Although haematological malignancies do not represent the most common cancer group in the Western world, you can nonetheless study them very well. Leukaemia cells can be readily isolated with a needle in a vein and subsequently purified, cultured, frozen, and thawed. You can then perform a variety of different studies, including protein and DNA analysis. Each time, there are new research questions to address and technologies to apply. This is what I really love. While studying leukaemia cells and solving problems in leukaemia, one also gathers knowledge about other malignancies.

Q2 As the Program Director of the EHA 2021, what are the primary goals the EHA board is working towards in this year's congress? What strategies has the committee put in place to ensure these goals are achieved?

The EHA congress is a big meeting. At the annual in-person congresses, we would often have between 10,000 and 15,000 healthcare professionals and scientists in attendance. However, the virtual conferences are capable of attracting an even larger audience. Last year, over 25,000 people registered. Importantly, all these individuals are from different fields.

As such, EHA creates a platform for clinical, translational, and laboratory-based scientists to share their latest research, treatment strategies, and diagnostic tools. There is also an emphasis on breakthroughs in basic science.

Although I am based in the laboratory, I always make the effort to learn from my physician colleagues. In turn, I hope that my physician colleagues do the same, and attend the talks given by experimental scientists. Only when the haematology community comes together in this way can we begin to make the crucial breakthroughs and advances.

Q3 How much of an impact do you believe the EHA congress has, both directly on haematologists and indirectly on patients? Additionally, what sessions are you looking forward to in this year's congress and why?

As I previously mentioned, the EHA congress is where clinicians and academics come to present the most recent data from across the discipline. There is even a late-breaking session, where last-minute data can be submitted. As a consequence, there are treatments available nowadays that were unheard of 4 or 5 years ago.

To be honest, there are not just one or two specific talks but rather a number of them that I am looking forward to. The EHA in-focus sessions, which this year will cover topics such as immunotherapy and CRISPR-Cas9 technology for genome editing, are always of particular interest to me. The same is true of the COVID-19 talks, which will be presented by internationally renowned experts in the field.

Q4 As an active member of several scientific committees in haematology, such as EHA and American Society of Hematology (ASH), have you found similarities or differences in working in haematology between the European and American societies?

Overall, I would say that the EHA is slightly more clinically oriented than the ASH. However, they are both fantastic organisations that organise their own meetings separately but also work closely with one another on certain topics. I have visited both meetings many times and given presentations at both EHA and ASH, and the same is true for many of my peers.

In addition, these two societies offer a joint training programme for young scientists, which has been in place for 15 years. It is also worth mentioning that the EHA always dedicates 1 hour to specifically focus on its connection with ASH and other haematology organisations, including the Japanese Society of Hematology (JSH) and the International Society for Experimental Hematology (ISEH).

Q5 What do you believe are currently the biggest challenges facing the haematological research community? Are there any innovations on the horizon in the field of haematology that you think are particularly noteworthy?

Perhaps one of the biggest challenges is the impact of COVID-19 infections on coagulation; however, this is not my field of research.

Immunotherapy is an evolving and promising form of cancer treatment, which is being used more and more in the haematological malignancies. Improvements in molecular biological techniques also deserve a mention since these allow investigators to generate cellular therapies. In fact, a very nice example was presented at this year's EHA. Young patients who were born with so-called Hurler's disease were treated using gene therapy, in which a genetic defect was restored in the cells of those patients. Of course, the long-term effects of those treatments need investigating; however, this is one of those examples which makes our work so exciting.

Q6 As an educator, what advice would you give to students interested in pursuing a career in haematology?

Individuals who have a clinical background should always try to understand the role played by laboratory-based scientists. Similarly, scientists that are active in our field should always be aware of the needs in the clinic. Although less specific to the field of haematology, I also think it is important to remember that, as an individual, you do not know everything yourself. There are always opportunities to learn from others: your tutors, collaborators, scientists from different disciplines, and your wider network. Importantly, others in your network should also learn from the knowledge and wisdom you have accrued. It is often the case that you can benefit from others just as much as they can benefit from you. This multidisciplinary approach has made our field of research even more interesting and attractive than it was 10 or 15 years ago. ■

EHA-ESMO Guidelines for the Diagnosis, Treatment, and Follow-up of Multiple Myeloma

Theo Wolf

Editorial Assistant

Citation: EMJ Hematol. 2021;9[1]:28-31.

ON DAY 6 of the European Hematology Association (EHA) Virtual Congress 2021, Pieter Sonneveld, Professor of Hematology, Erasmus MC Cancer Institute, Rotterdam, the Netherlands, chaired the European Society for Medical Oncology and EHA (ESMO-EHA) joint session on clinical practice guidelines for the diagnosis, treatment, and follow-up of multiple myeloma.

NEWLY DIAGNOSED MULTIPLE MYELOMA

Maria Gavriatopoulou, Assistant Professor of Therapeutics and Clinical Trials Methodology, National and Kapodistrian University of Athens, Greece, started by presenting the case of a 78-year-old male patient with a history of arterial hypertension, coronary artery disease, benign prostatic hyperplasia, and chronic obstructive pulmonary disease. The patient was diagnosed with mild anaemia by his general practitioner three months prior to being admitted to the hospital emergency department due to fatigue, bone pain, and mild fever. On admission, Gavriatopoulou noted that the patient's haemoglobin level was 8.2 g/dL; platelet and white blood cell levels were normal; serum creatinine and calcium levels were increased; albumin level was decreased; and the total protein level was within normal range. A bone marrow aspirate and biopsy were performed, showing a monoclonal plasma cell infiltration of 90% and a plasmablast infiltration of approximately 10%. According to Gavriatopoulou, the serum M-spike was 4 g/dL, serum immunofixation was positive for IgGκ, and urine-peak was 862 mg per 24 hours. A whole-body CT found multiple lytic lesions throughout the spine, compression fractures of the eleventh thoracic and second and fourth lumbar vertebra, and a paraosseous mass in the pelvis. Next, Gavriatopoulou highlighted the results of the fluorescence *in situ* hybridisation (FISH) studies: the t(4;14) translocation was expressed in 96% of myeloma cells and the β2-microglobulin level was substantially elevated (9.9 mg/L). The patient was therefore classified as International Staging System (ISS) III and Revised International Staging System (R-ISS) III. Gavriatopoulou then provided an overview of the five therapeutic options available at the time: lenalidomide plus dexamethasone (Rd); bortezomib, melphalan, and prednisone (VMP); bortezomib, cyclophosphamide, and dexamethasone (VCd); modified lenalidomide, bortezomib, and dexamethasone (VRd-lite);

"The major discriminant at the time of diagnosis is eligibility for autologous stem cell transplantation."

or daratumumab plus bortezomib, melphalan, and prednisone (Dara-VMP [in the context of a clinical trial]). Gavriatopoulou revealed that the patient was enrolled in the ALCYONE study and randomised to the Dara-VMP arm. If the patient progresses on Dara-VMP, potential options in the future include re-institution of bortezomib (with or without a third agent), starting Rd, adding Rd to daratumumab, considering lenalidomide plus dexamethasone, or switching to an isatuximab combination.

The second case presentation documented by Gavriatopoulou concerned a 69-year-old female. The patient had a haemoglobin level of 8.6 g/dL; creatinine and calcium were both within the normal range; β2-microglobulin was increased; albumin level was decreased; and lactate dehydrogenase levels were within the normal range. The bone marrow biopsy revealed a plasma cell infiltration of 65%. Furthermore, FISH testing was positive for deletion 17p (in 40% of the plasma cells) and negative for translocation t(4;14), translocation t(14;16), and add1q. Whole-body low-dose CT revealed multiple lytic lesions in the thoracic and lumbar vertebrae as well as in the pelvis; however, there were no fractures or extraosseous mass. Gavriatopoulou stated that the patient (classified as ISS Stage III and R-ISS Stage III) was initially treated with bortezomib, lenalidomide, and dexamethasone (VRd) for eight cycles and achieved very good partial remission. Due to the presence of deletion 17p, the patient received maintenance with bortezomib (every 15 days) and lenalidomide, and remained in very good partial remission for 19 months. Despite this, the patient eventually relapsed, with severe anaemia, a plasma cell infiltration of 55% in the bone marrow, and skin and liver extramedullary disease. Consequently, the patient received second-line therapy with daratumumab plus carfilzomib and dexamethasone (D-Kd) and achieved haematological partial remission, disappearance of skin plasmacytomas, and a 60% reduction in liver disease. Carfilzomib was discontinued after seven cycles because of uncontrolled hypertension. The patient progressed again, with new skin plasmacytomas and an increase in liver disease. Belantamab mafodotin was utilised in the third-line setting, and the patient achieved a haematological partial remission, partial remission in liver plasmacytomas, and disappearance of skin plasmacytomas. One of the main adverse events reported was ocular toxicity, which completely resolved when treatment was interrupted and supportive care was administered. This did not re-occur upon treatment re-initiation at a reduced dose level.

FRONT-LINE TREATMENT

Francesca Gay, Associate Professor of Hematology, University of Turin, Italy, started by summarising the treatment algorithm for people with newly diagnosed multiple myeloma. The major discriminant at the time of diagnosis is eligibility for autologous stem cell transplantation (ASCT). In terms of induction therapy, transplant-eligible patients are administered either VRd or daratumumab plus bortezomib, thalidomide, and dexamethasone (Dara-VTd). If neither of these options are available, VTd or VCd can be used instead. Thereafter, the standard treatment is autologous transplant with high-dose (200 mg/m^2) melphalan. Lastly, lenalidomide is given as maintenance. In patients who are not eligible for ASCT, such as those featured in the previous presentation by Gavriatopoulou, there are three strategies considered as first-line options: Dara-Rd, Dara-VMP, and VRd. When Dara-Rd and Dara-VMP are not available, VRd is the preferred option in fit patients. Alternatively, Rd and VMP may be considered for individuals who cannot receive the previous regimens.

According to Gay, ASCT eligibility is based on a patient's age (>70 years) and the absence of co-morbidities. VRd is likely to offer the best risk–benefit profile among triplets based on bortezomib; however, this treatment regimen lacks a Phase III randomised head-to-head comparison with VTd and is not licensed by the European Medicines Agency (EMA).

"The four-drug combination Dara-VTd is more efficacious than VTd and is the new standard of care."

The four-drug combination Dara-VTd is more efficacious than VTd and is the new standard of care. Induction with between four and six cycles is the recommended approach. Regarding consolidation therapy post-ASCT, Gay acknowledged that this is not currently considered as an option in the guidelines. Even so, two cycles of VRd should be considered in patients who received VCd induction. Additionally, tandem ASCT is recommended for patients with high-risk disease or in patients who received VCd introduction. Finally, Gay stressed that allogeneic stem cell transplantation does not offer overall survival benefit relative to tandem ASCT. With respect to maintenance, lenalidomide is considered the standard of care for all patients with multiple myeloma post-ASCT. Furthermore, bortezomib may be considered for individuals with high-risk disease. Ixazomib maintenance in the post-ASCT setting offers progression-free survival (PFS) benefit over placebo but has not yet been approved by the EMA or U.S. Food and Drug Administration (FDA).

TREATMENT OF PATIENTS WITH RELAPSED OR REFRACTORY MULTIPLE MYELOMA

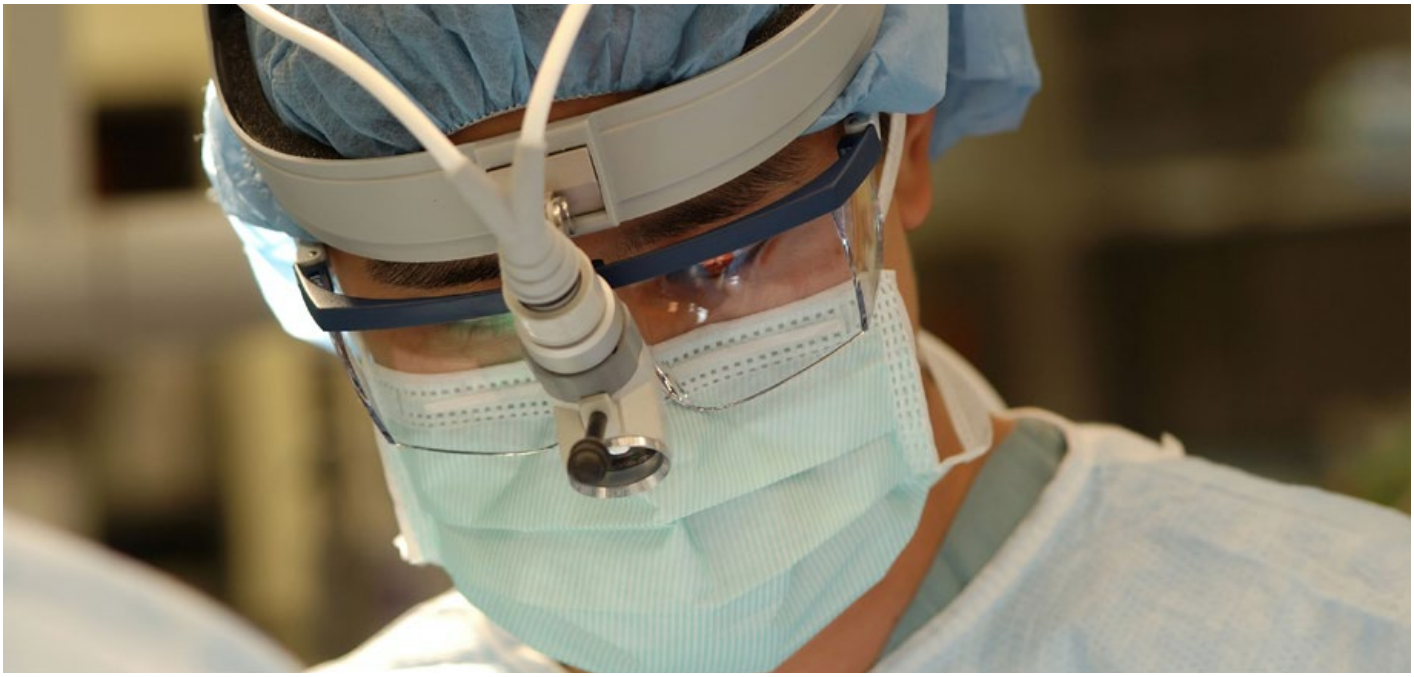
Meletios Dimopoulos, Professor of Hematology and Oncology, National and Kapodistrian University of Athens, begun by explaining that there are a number of factors to consider when selecting treatment at relapse. These include patient-related factors such as age, frailty, and performance status; the presence of comorbidities, renal insufficiency, or hepatic impairment; and preference on the mode of administration. Important treatment-related factors include the expected efficacy and toxicity of the proposed therapy, bone marrow reserve, the type of prior therapies and prior response, and the prior therapy-related toxicity. Lastly, disease-related factors (e.g., the aggressiveness of the current relapse or presence of refractory disease) also need to be considered.

Dimopoulos highlighted that there are several established regimens available for

lenalidomide-naïve or -sensitive patients. For example, the combination of carfilzomib, lenalidomide, and dexamethasone is associated with an improved PFS and overall survival. Moreover, Dara-Rd is an effective regimen in the second-line setting. Finally, elotuzumab- and ixazomib-Rd have been used in certain patient subpopulations (i.e., elderly individuals). However, Dimopoulos emphasised that one of the major concerns is refractoriness to lenalidomide. Data from the ENDEAVOR trial illustrated that carfilzomib in combination with dexamethasone was associated with a median PFS of approximately 9 months in patients who were lenalidomide-refractory. A similar length of PFS was observed in the CASTOR trial, where daratumumab was combined with bortezomib and dexamethasone. Clearly, these are not very promising data. Dimopoulos focused on more recent studies that have provided better results. For instance, in the OPTIMISMM trial, pomalidomide, bortezomib, and dexamethasone (PVd) showed superior efficacy relative to bortezomib plus dexamethasone in patients with relapsed or refractory multiple myeloma previously exposed to lenalidomide. When using PVd, the median PFS for individuals progressing on lenalidomide was in excess of 18 months. According to Dimopoulos, the most robust data for this specific subset of patients have come from the CANDOR and IKEMA studies, which both have a common design and investigational arm (using carfilzomib at the standard dose of 56 mg/m^2 with dexamethasone). In the counter-trial, there was addition of daratumumab (CANDOR) or isatuximab (IKEMA). The counter-trial showed that the median PFS for patients who progressed on lenalidomide was 28 months.

Dimopoulos also outlined possible treatment options for anti-CD38 and lenalidomide pre-treated or refractory individuals. Data from the BOSTON trial, where selinexor, bortezomib, and dexamethasone has been used, showed high response rates and low rates of peripheral neuropathy. Likewise, a combination of venetoclax, bortezomib, and dexamethasone exhibited promising clinical efficacy with acceptable tolerability and safety in the BELLINI trial.

Dimopoulos outlined the EHA-EMSO 2021 recommendations for second and subsequent relapses. Combinations of pomalidomide, low-dose dexamethasone and either isatuximab (ICARIA-MM study) or daratumumab (APOLLO study) significantly improved PFS in people with relapsed or refractory multiply myeloma. With regard to newer regimens, Dimopoulos revealed that belantamab mafodotin has been approved in the European Union (EU) for use as monotherapy in individuals who have failed all other treatment options (penta-refractory patients). ■



Antibody Levels in COVID-19 Affected by Age, Gender, and Disease

Heeral Patel
Editorial Assistant

Citation: EMJ Hematol. 2021;9[1]:32-34.

AT THE EUROPEAN Hematology Association (EHA) 2021 Virtual Congress, Evangelos Terpos, University of Athens School of Medicine, Greece, discussed COVID-19 and how neutralising antibody levels are affected by various factors such as age, gender, and disease.

The COVID-19 pandemic has been a catalyst for rapid vaccine development by scientists and researchers around the globe compared to the usual time frame. From bench to bedside, the process of drug development can take up to 10 years; however, a global effort that involved pharmaceutical companies working collaboratively with international researchers has significantly accelerated the process. Despite the vaccine's high efficacy, there is still much more to learn about how individual groups respond to the vaccine.

"Not only were neutralising antibodies higher just before the second dose but they were much higher for the younger age group, aged 25–50 years, compared to the octogenarians, aged 80–95 years."

Terpos shared his thoughts regarding vaccination against COVID-19. Firstly, Terpos discussed the differences in efficacy between the most popular mRNA vaccines: BNT162B2 (Pfizer-BioNTech), mRNA-1273 (Moderna), AZD1222 (AstraZeneca), and Ad26.COV2.S (Johnson & Johnson). The vaccines by Pfizer-BioNTech and Moderna have the highest efficacy of >90%, whereas the latter two have a slightly lower efficacy rate: 70–90%.

AGE- AND GENDER-DEPENDENT ANTIBODY RESPONSES

In light of this observation, Terpos expressed the importance of testing the vaccine in healthy populations. He shared his research from a recent study looking at age-dependent and gender-dependent antibody responses after the Pfizer-BioNTech vaccine. Interestingly, the groups involved in this study were the first to get vaccinated in Greece.

Firstly, Terpos recruited 225 health workers of a median age of 49 years and volunteering octogenarians of 85 years median age. The team measured the neutralising activity of antibodies at different stages of vaccination: one day before the vaccine (Day 1), eight days after the first dose, two weeks after the second dose, and four weeks after the second dose. Results showed that the two groups had no neutralising activity before the first dose and almost the same results 8 days after the first dose.

Interestingly this changed just before the second dose was administered. Data presented by Terpos demonstrated that, not only were neutralising antibodies higher just before the second dose but they were much higher for the younger age group, aged 25–50 years, compared to the octogenarians, aged 80–95 years. The neutralising antibody levels changed yet again after the second dose, with almost all groups showing very high antibody levels. Taken together, these results confirm that for those aged 50 years and above, the second dose is necessary. Intriguingly, neutralising antibody levels were also affected by gender. In the elder age group, females developed significantly more antibodies than males on Day 22 and Day 50. The results suggest that the levels of antibodies are gender-dependent in older individuals. The same was not concluded for the younger age group because, although antibody levels were higher in females, the results were not statistically significant.

"Antibody levels were initially higher; however, after Day 22 the levels were very similar in both cohorts, with a slight favour towards the Pfizer-BioNTech vaccine with a p value of 0.03."

Terpos shared unpublished data showing the results from this cohort after 90 days post-second dose. The data confirmed that although there was a slight decrease in neutralising antibodies compared to Day 36 and Day 50, no patient was recorded with antibody levels <30%, the level at which a person is considered COVID-19-positive. To better understand the significance of these results and the main factors for antibody production, the team used a machine learning analysis approach. The results showed that age is a negative factor to neutralising antibody levels in older age groups, confirming that younger individuals produced higher antibody levels. Terpos also looked at BMI but found that this had no impact in the levels of antibody; however, in previous studies, BMI has been shown to have a negative impact on antibody levels.

ANTIBODY LEVELS IN INDIVIDUALS PREVIOUSLY INFECTED WITH COVID-19

Following on from the initial research, it is vital to understand why the neutralising antibody levels on Day 1 were higher in some groups even before the first dose. Terpos believes this is because either they had previously been infected with COVID-19 or they had COVID-19 at the time without realising. After the first dose, the data showed that the antibody levels increased to a very high level and stayed that way even at Day 22. This suggests that this previously infected population may not need a second dose.

To comprehend why this may be, the levels of inflammatory cytokines were measured in the different groups. Those who had high neutralising antibodies on Day 1 also had high inflammatory cytokines on Day 2 (the day after the first dose), whereas those who did not have high levels of antibodies on Day 1 only showed a high inflammatory response after the second dose. Again, this reinforces the argument that those who had already been infected and had high neutralising antibodies may not need a second dose.

THE EFFECT OF HAEMATOLOGICAL MALIGNANCIES ON ANTIBODY LEVELS

An interesting question was raised by Terpos and his team as to whether there is a difference in neutralising antibody levels between the two most common vaccines distributed in Europe currently: BNT162B2 and AZD1222.

Antibody levels were initially higher in the Pfizer-BioNTech vaccine cohort; however, after Day 22 the levels were very similar in both cohorts,

with a slight favour towards the Pfizer-BioNTech vaccine with a p value of 0.03. After Day 50, antibody levels increased in the AstraZeneca vaccine suggesting that the second dose of the AZ vaccine can be given earlier; i.e., 6 or 8 weeks after the first dose.

After addressing the various factors that could affect the neutralising antibodies in healthy populations, the study assessed the antibody responses after vaccination in patients with haematological malignancies such as chronic lymphocytic leukaemia and multiple myeloma. Unfortunately, the results in these groups were not as promising. Patients with chronic lymphocytic leukaemia who were taking ibrutinib, bruton kinase inhibitors, or immune chemotherapy regimens had very low antibody responses compared to the healthy control group. Furthermore, 40% of these individuals did not develop neutralising antibodies against the virus. Similar outcomes were observed in patients with multiple myeloma. The types of drugs and treatment the patients were on seem to have had an impact on the levels of antibodies; this has also been shown in other diseases such as amyloid light-chain amyloidosis, low-grade lymphoproliferative malignancies, and other cancers.

In his concluding remarks, Terpos explained that these data confirmed that various factors affect the levels of neutralising antibodies including age, gender, and disease. Younger healthy individuals had higher neutralising antibodies compared to elder volunteering octogenarians. On top of this, neutralising antibody levels were also shown to be affected by the vaccine given (i.e., Pfizer-BioNTech versus AstraZeneca) as well as by patient comorbidities (e.g., patients undergoing treatment for cancer and other conditions). This leads to further questions: do certain individuals need a second dose and do individuals who do not have an antibody response at all need a third dose? These unanswered questions open the door for future research and may help us understand how to improve vaccination delivery.

Abstract Reviews

Sharing insights from abstracts presented at the European Hematology Association (EHA) 2021 Virtual Congress, global haematologists and researchers have provided these summaries of their fascinating studies.

COVID-19 in Patients with Acute Leukaemia: The Experience of a Haematological Centre

Authors: *Alessandra Malato, Antonino Mulè, Valeria Calafiore, Francesco Di Bassiano, Roberto Mauro, Clotilde Cangialosi, Ugo Biondo, Caterina Patti

UOC di OncoEmatologia, Ospedali Riuniti Villa Sofia-Cervello, Palermo, Italy
*Correspondence to alessandramalato@hotmail.com

Disclosure: The authors have declared no conflicts of interest.

Keywords: Acute leukaemia, COVID-19.

Citation: EMJ Hematol. 2021;9[1]:35-37. Abstract Review No. AR1.

BACKGROUND AND AIMS

Patients with haematologic malignancies appear to have a greater risk of severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) infection and severe disease due to myelosuppression.[1-3] Furthermore, delays in treatment of patients with haematologic malignancies, especially those with acute leukaemia planned for chemotherapy or transplantation, are associated with a risk of disease progression. To date, some societies recommend that chemotherapy should generally not be started until COVID-19 symptoms have completely resolved and viral testing becomes negative. However, implications of the aforementioned recommendations remain uncertain in routine clinical practice, and data on COVID-19 in patients with haematologic malignancies are still limited.

MATERIALS AND METHODS

From February 2020 to February 2021, there was a total of 310 hospitalisations, where 163 adult patients were admitted to the authors' centre for treatment of haematologic malignancies. The indication for admission was acute myeloid leukaemia (AML) in 50 (30%) patients, acute lymphoblastic leukaemia in 14 (8%), lymphoma in 54 (33%), myeloma in 14 (8%), and 31 (19%) as other.

Table 1: Overview of patient characteristics.

ID	Age	Sex	Diagnosis	Time of COVID-19 infection	COVID-19 complications	Change or delay in the haematological treatment	Days delay	Deaths owing to COVID-19	Remission status after current therapy
1	82	M	AML	Not yet treated	Progressive respiratory failure	No treatment	N/A	Died owing to progressive respiratory failure before treatment could be started	N/A
2	56	F	AML	In peak cytopenia post I consolidation	None	Delay	60	No	CR
3	62	M	AML	Relapsed post I induction	Progressive respiratory failure	N/A	N/A	Died owing to progressive respiratory failure	N/A
4	64	M	AML	In peak cytopenia post re-induction	Interstitial pneumonia	Delay	30	No	CR
5	53	M	AML	In peak cytopenia post I induction	None	Delay	10	No	In peak cytopenia after allo-BMT
6	67	F	AML	Relapsed post I induction	DVT-PE; interstitial pneumonia	Delay	30	No	CR, scheduled for allo-BMT
7	62	F	AML	In peak cytopenia post I consolidation	Interstitial pneumonia	Delay	40	No	CR
8	66	M	ALL Ph-	In peak cytopenia post I consolidation	Interstitial pneumonia	Delay	50	No	CR
9	21	M	ALL Ph-	CR post II consolidation	None	Delay	20	No	CR
10	59	M	AML	Refractory to I induction	Progressive Died owing to progressive	N/A	N/A	Died owing to progressive respiratory failure	N/A

Allo-BMT: allogeneic bone marrow transplant; ALL-Ph: acute lymphoblastic leukaemia Philadelphia (negative/positive); AML: acute myeloid leukaemia; CR: complete remission; DVT-PE: deep vein thrombosis-pulmonary embolism; F: female; M; male; N/A: not applicable.

Diagnosis of SARS-CoV-2 infection was based on virus detection by real-time polymerase chain reaction (SARS-CoV-2 E-gene RT-PCR) in respiratory tract specimens. Standard preventive measures for SARS-CoV-2 infection control were applied to the care of all patients, in accordance with national disease control and prevention guidelines.

RESULTS

Ten (6%) patients tested positive for SARS-CoV-2 via PCR in a unique COVID-19 outbreak during hospitalisation stay, and they were immediately transferred to the COVID Infectious Unit. All of these patients were affected by acute leukaemia (eight patients with AML; two patients with acute lymphoblastic leukaemia, Philadelphia chromosome-negative). Most patients were at the peak of cytopenia at the time of their COVID-19 infection. Nine patients had been treated with intensive chemotherapy before SARS-CoV-2 confirmation.

At SARS-CoV-2 diagnosis, one patient had untreated, newly diagnosed AML while three patients had refractory/relapsed AML. One patient was in complete remission with incomplete haematologic recovery. Deep vein thrombosis complicated by pulmonary embolism and interstitial pneumonia was observed in a patient despite anticoagulation and thrombocytopenia. After SARS-CoV-2 infection, no leukaemia-specific treatment was adjusted.

Three patients (30%) died due to severe acute respiratory distress syndrome despite extracorporeal membrane oxygenation in deep aplasia; all of these patients had refractory disease. Seven patients were delayed in receiving chemotherapy treatment for 34 days; chemotherapy started once COVID-19 symptoms had been completely resolved and two viral tests became negative. These patients maintained their complete remission and remained negative for SARS-CoV-2. One patient underwent bone marrow transplantation.

CONCLUSION

The authors' findings support the vulnerability of patients with haematologic malignancies in the COVID-19 pandemic, and reported a high COVID-19 infection mortality of 30%, in accordance with other haematological case series. However, deaths owing to COVID-19 were observed in patients with leukaemia disease progression. Furthermore, the patients who recovered from COVID-19 in leukaemia remained negative for SARS-CoV-2 after delivery of chemotherapy and underwent their following chemotherapy and allogeneic bone marrow transplantation programme without any other complications. ■

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Hepcidin, the Main Regulator of Iron Homeostasis, is a Marker of COVID-19 Severity and Mortality in a Cohort of Hospitalised Italian Patients

Authors: Antonella Nai,[1,2] Nicola Ivan Lorè,[3] Alessia Pagani,[1] Rebecca De Lorenzo,[2] Simona Di Modica,[1] Fabio Saliu,[3] Daniela Maria Cirillo,[3] Patrizia Rovere-Querini,[2,4] Angelo Manfredi,[2,5] *Laura Silvestri[1,2]

1. Regulation of Iron Metabolism Unit-Div. Genetics & Cell Biology-IRCCS San Raffaele Scientific Institute, Milano, Italy
2. San Raffaele Vita-Salute University, Milano, Italy
3. Emerging Bacterial Pathogens Unit-IRCCS San Raffaele Scientific Institute, Milano, Italy
4. Division of Immunology, Transplantation and Infectious Diseases-IRCCS San Raffaele Scientific Institute, Milano, Italy
5. Unit of Immunology, Rheumatology, Allergy and Rare Diseases, IRCCS San Raffaele Scientific Institute, Milano, Italy

*Correspondence to silvestri.laura@hsr.it

Disclosure: The authors have declared no conflicts of interest.

Acknowledgements: This work was supported by a COVID-19 programme project grant from the IRCCS San Raffaele Hospital and by the grant COVID-2020-12371617 from the Italian Ministero della Salute. The authors would like to thank the patients for their generous collaboration to our research projects; and Clara Camaschella for valuable criticism and advice. The authors are indebted to Fabio Ciceri, responsible for the San Raffaele Biobank; and would like to thank Cristina Tresoldi and all people working at the Institutional Biobank, whose generous support made it possible to carry out these studies. The contribution of the "Biob angels" of the San Raffaele in the recovery and transport of biological samples is also recognised with gratitude.

Keywords: COVID-19, hepcidin, inflammation, iron.

Citation: EMJ Hematol. 2021;9[1]: 38-39. Abstract Review No. AR2.

BACKGROUND AND AIMS

The clinical spectrum of severe COVID-19, the recently described systemic disease caused by severe acute respiratory coronavirus 2 (SARS-CoV-2) infection, is characterised by the acute activation of the innate immune system accompanied by a prothrombotic state, and ranges from asymptomatic cases to respiratory failure. Unfortunately, precise biomarkers that predict COVID-19 outcome are still lacking. Several risk factors for SARS-CoV-2 infection are well established, including advanced age, male sex, strong inflammatory response, neutropenia and lymphopenia, and more recently hypoferraemia. At present, few data are available on the possible contribution of deranged iron homeostasis on COVID-19. In a retrospective study serum iron was found to be extremely low in most COVID-19 cases and a predictor of mortality.[1] In addition, decreased serum iron was associated with hypoxaemia in patients with severe COVID-19 in the intensive care unit (ICU).[2] More recently, hypoferraemia was associated with increased hospitalisation and oxygen demand in German patients with COVID-19.[3]

Hepcidin, the liver peptide hormone that regulates plasma iron concentration by blocking ferroportin function,[4] is at the crossroad between iron metabolism and inflammation, being positively regulated by iron itself and proinflammatory cytokines,[5] and may represent the link between iron deficiency and COVID-19 severity. However, its role as a potential biomarker of COVID-19 severity has not been explored in depth.

The aim of this study was to investigate whether plasma hepcidin, measured at admission, could be considered a marker of COVID-19 severity and mortality.[6]

MATERIALS AND METHODS

Plasma hepcidin and iron levels were analysed in a well-characterised cohort of 111 Italian patients with COVID-19 hospitalised between 18th March and 5th May, 2020, at San Raffaele University Hospital in Milan, Italy, one regional COVID-19 reference hospital. Diagnosis of COVID-19 was based on a positive real-time reverse-transcriptase PCR (RT-PCR) from a nasal and/or

throat swab together with signs, symptoms, and/or radiological findings suggestive of COVID-19. The present study was part of a more extensive monocentric observational cohort study, the Covid-BioB study, implemented at San Raffaele University Hospital.[7] The cohort had a median age of 57.6 (48.5–66.3) years, and included predominantly males (64%). Blood samples were obtained at admission, and plasma was immediately retrieved and frozen until analysed for the concentration of iron, hepcidin (ELISA kit from Intrinsic LifeSciences), proinflammatory markers as C-reactive protein (CRP) and ferritin, and cytokines with a role in hepcidin modulation, as IL-6, IL-1b, TNFα and IFN-γ.[6]

RESULTS

In this cohort of patients with COVID-19, iron concentration was below normal range in 93.7% of patients, whereas hepcidin levels were significantly increased in 61.3% of patients. However, considering that hypoferraemia suppresses hepcidin expression, even normal hepcidin is inappropriately high in most cases. Patients with higher hepcidin levels were significantly older and had higher concentrations of markers of inflammation (CRP and ferritin) and cell damage (AST and LDH). Negative correlations were observed with the severity of respiratory failure, as reflected by the PaO_2/FiO_2 ratio. The role of high hepcidin levels is strengthened by the Kaplan–Meier survival curve and confirmed by the regression tree analysis, which identified hepcidin as the most important predictor of death among the others recognised predictors. On the other hand, iron levels do not affect survival, likely because of the uniformly low levels in all patients. Interestingly, limiting the analysis to critical patients in ICU, high hepcidin predicts mortality, independently of age, lung function, inflammation, and tissue damage.[6]

CONCLUSION

Overall, these data suggest that hepcidin can be considered a marker of morbidity and outcome of COVID-19, of special value for severely compromised patients in ICU.[6] Further studies are needed to verify whether targeting the hepcidin axis may influence the disease outcome. ■

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Determination of Cut-Off Optimal Values of Ten Haematological Formulas in the Distinction Between Iron Deficiency Anaemia and β-Thalassaemia Minor

Authors: Aya Chakroun,[1,2] Mayssa Ben Ayed,[1,2] *Hela Baccouche,[1,2] Sonia Mahjoub,[1,2] Neila Ben Romdhan[1,2]

1. Hematology Department, La Rabta University Hospital, Tunis, Tunisia
2. Faculty of Medicine of Tunis, Tunis El Manar University, Tunisia

*Correspondence to hela_baccouche@yahoo.fr

Disclosure: The authors have declared no conflicts of interest.

Acknowledgements: The authors would like to thank Syrine Saffar, Amani Jabri, and Maroua Chelli for data acquisition.

Keywords: Anaemia, β-thalassaemia, index, threshold.

Citation: EMJ Hematol. 2021;9[1]:40-41. Abstract Review No. AR3.

BACKGROUND AND AIMS

Anaemia is a public health problem. Two aetiologies of microcytic anaemia are relatively common in Tunisia: iron deficiency anaemia (IDA) and β-thalassaemia minor (βTM). To guide the clinician in discriminating IDA from βTM, several studies have developed indices and formulas based on blood count parameters determined by haematology analysers. The aim of this study was to evaluate the performance of these formulas to discriminate βTM and IDA and to identify the cut-off values adapted to the studied population for each formula.

MATERIALS AND METHODS

After reviewing the records of adult patients with IDA and βTM, two groups were formed (IDA: n=172; and βTM: n=69). Demographic and blood count data were recorded. Performances of ten formulas and indices reported in the literature in the discrimination between IDA and βTM were studied. Statistical analysis was performed using SPSS® Statistics (version 19.0; IBM, Armonk, New York, USA). Sensitivity (Se), specificity (Sp), likelihood ratios, predictive values, and analysis of receiver operative characteristic curves were carried out. For each formula, optimal cut-off values were determined according to the Youden index. The study was conducted in accordance with the Helsinki declaration. No personal identification data were collected.

RESULTS

The haemoglobin rate, the erythrocyte count, and the red blood cell distribution index by standard deviation parameters showed an excellent discriminating power (area under the curve [AUC]: 0.913, 0.971, and 0.968, respectively). Performance assessment of the various original cut-off indices showed that Green and King (G&K) index (Se: 71.01%; Sp: 97.67%; AUC: 0.96), red cell distribution width (RDW) index (Se: 78.26%; Sp: 97.67%; AUC: 0.95), and Sirdah index (Se: 76.81%; Sp: 97.67%; AUC: 0.965) were reliable. At the new cut-off, the England and Fraser (E&F), G&K, Sirdah, and RDW indices were the most effective in diagnosing βTM (Table 1). At these new thresholds, both E&F and Sirdah indices showed a gain in Se and accuracy.

In accordance to these results, recent study and meta-analysis proved that the erythrocyte count was an effective discrimination tool for IDA and βTM at a cut-off value of >5x10^6/mm^3 with an AUC of 0.921;[1,2] however, discrepant results with much lower performances were found.[3] At original cut-offs, many studies showed the limited performance of the Shine and Lal (S&L) formula.[3,4] In the Tunisian study of Sahli et al.[5] the S&L formula provided a Se of 98% but a Sp of 50%.[5] The meta-analysis of Hoffman et al.[6] stated that the S&L formula would be preferred in a Mediterranean population, in addition to the Mentzer and Sirdah indices. Considering new respective cut-off values of all indices studied, only E&F, G&K, RDW, and Sirdah indices showed AUCs >0.8, high likelihood ratios, and accuracy >90%.

Table 1: Performance of the new respective indices cut-off values in the discrimination of β-thalassaemia minor and iron deficiency anaemia.

Formula	βTM cut-off	J	Proposed βTM cut-off for our population	Se (%)	Sp (%)	LR+	LR-	Accuracy (%)
E&F	0	0.84	<9.17	91.30	93.61	14.28	0.09	92.9
G&K	65	0.83	<75.50	86.95	96.00	21.73	0.13	93.3
Mentzer	13	0.72	<14.01	88.40	83.73	5.43	0.14	85.1
RDW	220	0.82	<248.95	89.85	92.50	11.98	0.11	91.7
Ricerca	4.4	0.72	<3.60	81.15	91.30	9.33	0.21	87.9
Srivastava	3.8	0.55	<4.07	78.20	76.80	3.37	0.28	76.7
S&L	1,530	0.35	<771.71	71.00	64.50	2.00	0.45	66.4
Ehsani	15	0.71	<14.45	79.70	91.90	9.84	0.22	88.4
Sirdah	27	0.84	<31.31	89.85	94.20	15.49	0.10	92.9
Sehgal	972	0.67	<766.10	75.36	92.50	10.05	0.27	87.5

βTM: beta-thalassaemia minor; E&F: England and Frazer index; G&K: Green and King index; J: Youden index; LR: likelihood ratio; RDW: red blood cell distribution width; Se: sensitivity; Sp: specificity; S&L: Shine and Lal index.

These findings were consistent with many studies conducted in Spanish, Iranian, and Indian populations.[4,7,8] In Tunisia, there is no national thalassaemia screening programme as in some countries.[9,10] Moreover, very few Tunisian studies on the assessment of these formulas are published. The reliability of Mentzer and Srivastava indices (with an accuracy of 85% and 94%, respectively) with an AUC >0.9 of the new proposed cut-offs was reported.[5]

CONCLUSION

The adoption of population-specific cut-offs helps to improve the performance of these formulas and indices and could considerably reduce unnecessary iron therapy and diagnostic expenses. The technology deployed by haematology analysers and some clinical data would be necessary for optimal diagnostic guidance. ■

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Allogeneic Peripheral Blood Stem Cell Transplantation in 34 Patients with Myelodysplastic Syndrome

Authors: Sabrina Akhrouf, *Malek Benakli, Amina Talbi, Imane Abderrahim, Rihab Benouattas, Farih Mehdid, Rachida Belhadj, Nadia Rahmoune, Mounira Baazizi, Dina Ait Ouali, Hanane Bouarab, Sara Zerkout, Fouzia Louar, Rose-Marie Hamladji, Redhouane Ahmed Nacer

Hematology and Bone Marrow Transplant Department, Pierre and Marie Curie Center, Algiers, Algeria
*Correspondence to malekbenakli@gmail.com

Disclosure: The authors have declared no conflicts of interest.

Keywords: Allogeneic blood stem cell transplantation, myelodysplastic syndromes (MDS).

Citation: EMJ Hematol. 2021;9[1]:42-43. Abstract Review No. AR4.

BACKGROUND AND AIMS

Myelodysplastic syndromes (MDS) are clonal haematopoietic disorders of pluripotent stem cells, characterised by ineffective haematopoiesis and rich marrow dysplasia resulting in cytopenias. In addition, MDS frequently progresses to acute myeloid leukaemia and is the most common pre-leukaemic state in adults.[1,2] Allogeneic haematopoietic stem cell transplantation (HSCT) is currently the only potentially curative therapy for MDS. It can be performed in patients aged <60 years from an HLA-compatible or haplo-identical donor.[3-5]

MATERIALS AND METHODS

Between May 2001 and March 2019 (18-year period), 34 patients with MDS underwent allogeneic HSCT in the authors' centre (geno-identical: 31 patients; haplo-identical: 3 patients).[6] The median age of the patients was 36 years (4–58) and the sex ratio was 1.42 (20 males to 14 females). Median time from diagnosis to allogeneic HSCT was 11 months (2–81). According to the World Health Organization (WHO) 2016 classification, these were the pre-transplant statuses of the patients: MDS with uni-lineage dysplasia: 4, including 2 with ring sideroblasts and 1 with isolated deletion 5q; and MDS with multilineage dysplasia: 30, including 7 with excess blasts-1 and 9 with excess blasts-2. Various treatments had been received before the transplants: cyclosporin: 7 patients; erythropoietin: 7 patients; danazol: 3 patients; lenalidomide: 2 patients; azacitidine: 1 patient; aracytine: 1 patient; and rituximab: 1 patient. Thirty-three patients were transfusion-dependent before the graft, with an average of 32 red blood cells units per patient (3–135). All patients received myeloablative conditioning (classic: 13 patients; fludarabine/busulfan-4: 21 patients). Graft-versus-host disease (GVHD) prophylaxis consisted of cyclosporin and methotrexate according to the Seattle protocol in 31 patients, of which 10 patients received anti-thymocyte globulin, while three patients received post-transplant cyclophosphamide and mycophenolate mofetil without methotrexate. All patients received granulocyte colony stimulating factor alone to mobilise peripheral blood stem cells, with a median CD34+ cell count of 7.62×10^6/kg (3.18–19.90). In addition to the cyclosporine graft, one patient received a bone marrow graft.

RESULTS

Neutropenia occurred in all patients and the median duration of aplasia was 14 days (7–31). Median time to achieve neutrophil count $>0.5 \times 10^9$/L was 14 days (11–25) and platelets $>20 \times 10^9$/L was 13 days (9–35). Thirty patients (88.2%) required a red blood cell transfusion (8.7 units/patient) and 31 patients (91.2%) needed platelet transfusions (6.6 units/patient). Three patients (8.8%) presented with veno-occlusive disease, one of which was severe. Grade II–IV acute GVHD was observed in 8/26 patients (30.7%) and chronic GVHD in 11/20 patients (55.0%) of whom five had an extensive form. Relapse was observed in 2/26 patients (7.7%) within 4–20 months post-transplant. On 31st July 2020, the median follow-up was 94.5 months

(16–202); 16 patients (47%) were still alive (15 patients in complete remission and one patient relapsed, on azacitidine) and 18 patients (53%) had died, including 17 patients (50%) of tissue-resident memory (early infection: six; thrombotic microangiopathy: one; acute GVHD: four; pneumopathy: two; fulminant hepatitis: one; and metabolic disorders: two) and one patient in relapse. The overall survival was 47%, event-free survival was 44%, and GVHD-free and relapse-free survival were 32%.

CONCLUSION

Allogeneic HSCT is a curative option for patients with MDS; it has a considerable risk for transplant-related mortality and morbidity. Late effects like GVHD and relapse remain major challenges in the care of these patients. In the authors' study, it was a curative option in 44% of patients with 16 years of follow-up. Of these patients, 32% are alive with a good quality of life. ■

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Diagnosis, Treatment, Impact, and Unmet Needs of People with Mycosis Fungoides and Sézary Syndrome

Interviewee: Richard Cowan

Cancer Research UK, The Christie NHS Foundation Trust, Manchester, UK

Disclosure: The interviewee has acted as a consultant for Kyowa Kirin International.

Acknowledgements: Writing assistance was provided by Eleanor Roberts, Beeline Science Communications, Ltd, London, UK.

Disclaimer: The opinions expressed in this article belong solely to the named author.

Support: The writing and editorial support were funded by Kyowa Kirin International.

Citation: EMJ Hematol. 2021;9[1]:45-49.

INTRODUCTION

Mycosis fungoides (MF) and Sézary syndrome (SS), two of the most-studied types of cutaneous T-cell lymphoma (CTCL), account for approximately 60% and 10% of CTCL cases, respectively.[1] EMJ sat down with Richard Cowan, an oncologist with The Christie NHS Foundation Trust, University of Manchester, Manchester, UK, with expertise in CTCL, to discuss MF and SS diagnoses and treatments, their impact on patients, and unmet needs.

PRESENTATION

CTCL is a rare type of non-Hodgkin lymphoma that presents in the skin, with a subset of patients presenting with or developing extracutaneous disease.[1] MF may appear as patches, plaques, and tumours or a mixture of these, and rarely with erythroderma. Lesions are usually confined to 'bathing trunk areas' under the arms and on the upper legs, with progression also occurring from one area to another.[2] In SS, there is widespread erythroderma and often lymphadenopathy.[2] CTCL has an incidence of approximately 1/120,000 people, as found in one USA study;[3] it most commonly starts in a person's mid-50s, and predominates in men.[4] While CTCL can be fatal, with survival times under 5 years for SS and advanced MF, for those with early-stage MF, life span may be normal.[5]

In early MF especially, the clinical appearance may be misdiagnosed as eczema, psoriasis, or a fungal infection, leading to a median diagnostic delay of 36 months.[4] CTCL can also be difficult to diagnose histopathologically, explained Cowan, as lymphocyte infiltration in biopsied skin can be seen in many inflammatory conditions. Cell surface receptor expression analysis can reveal CD4+/CD7- and/or CD4+/CD26- neoplastic cells.[6] Cellular atypia and the characteristic distribution of these cells such as epidermotropism or tagging can be helpful in diagnosis. Cell surface expression analysis can reveal loss of certain T-cell antigens such as CD5 and CD7; such changes are indicative but not diagnostic.

Blood involvement may affect up to one in five early-stage patients and has been linked with worse outcomes and a higher risk of disease progression.[4,7] Therefore, quantification of blood tumour burden is important and should be used for staging, tracking therapeutic response, and monitoring for disease progression:[8] B0 (<250 cells/mL) signifies no significant blood involvement; B1 (≥250 and <1,000 cells/mL) is classified as low blood

tumour burden; and B2 (≥1,000 cells/mL) indicates a high blood tumour burden. B2 is synonymous with SS, which can alternatively be diagnosed by detection of a CD4:CD8 ratio ≥10 and circulating T-cell clones with cerebriform nuclei.[6,9]

THE IMPACT OF CUTANEOUS T-CELL LYMPHOMA

"We must stop and think what [CTCL] must be like day in, day out to realise the impact," Cowan stressed. Symptoms "set patients aside; they're either suffering physically or socially, and emotionally they're being distanced from 'normal' people." This has been confirmed in several studies.[10-12] Cowan highlighted how CTCL impact can occur at any stage: "We might see some in whom we consider the disease quite mild but we mustn't underestimate this: those patients too are suffering emotionally, [they are] self-conscious, embarrassed, and annoyed they can't get rid of this disease."

The extreme itchiness of CTCL, Cowan emphasised, "can be absolutely debilitating, interfering with sleep, work, and day-to-day life. We fail our patients miserably," he continued, "in that there is no good treatment for itch apart from treating the underlying condition." Regarding SS, Cowan discussed how additional problems include being very conscious of the bright red erythroderma, the distressing occurrence of continually flaking skin, and difficulties in maintaining core body temperature due to inflamed skin "emanating vast amounts of heat."

DIAGNOSIS

"GPs [general practitioners] rarely see CTCL," reported Cowan, and diagnostic delay may be both through misdiagnosis and because CTCL can initially respond to topical corticosteroids in a manner similar to more-common skin conditions.[2] It is usually only on progression that a dermatology referral occurs, although even general dermatologists and histopathologists may have little CTCL experience, explained Cowan.

A multidisciplinary team is needed for more complete diagnosis and management, comprising a CTCL-experienced dermatologist, a dermato- and haemato-pathologist experienced in skin and lymphoma, respectively, and an oncologist experienced in delivering CTCL-tailored treatments, discussed Cowan. He stressed the need for specialist nurses who have time to support patients and liaise with nursing care closer to home.

When it comes to making a diagnosis within this MDT, Cowan clarified: "Even with all the information, it's not infrequent for us to say: 'We're not sure.' It's a distressing situation for the patient who's come all the way to the specialist unit with the diagnosis of a malignant condition hanging over them and at the end of it all we say: 'We'll keep an eye on it'."

TREATMENT

CTCL treatment usually starts with skin-directed therapies such as topical corticosteroids or a topical mustine when available.[2,13] Twice-weekly narrow-band ultraviolet B phototherapy is the next option. This may be combined with oral psoralen, which Cowan reported can lead to a long-lasting response.[2,9,13] In MF, persistent local disease leads to radiotherapy,[2,9,13] to which CTLC lesions are "exquisitely sensitive," highlighted Cowan, so very low doses can be used, minimising side effects. With more widespread disease, total skin electron-beam therapy can be employed delivering low dose radiotherapy to the whole skin surface.[2,9,13]

The next treatment step is systemic therapy, with, according to Cowan, no one therapy standing out as first line. Options here include pegylated α-interferon, low-dose methotrexate, and the rexinoid bexarotene.[9] Immunotherapy is another systemic choice for more advanced disease, with the CD30-targeted agent brentuximab vedotin being efficacious in those with CD30+ CTCL.[2] Mogamulizumab has shown advantageous results[14] and is discussed further below. For SS, treatment can also include extracorporeal photopheresis administered on two consecutive days at specialised centres, repeated every 2 or 4 weeks.[6,15]

Advanced disease treatment can also involve chemotherapy, via CHOP (cyclophosphamide, doxorubicin, vincristine, oral prednisone), prolonged-release doxorubicin, or gemcitabine.[6]

However, Cowan noted that, while the response may be quick, it can be short-lived and require maintenance therapy. While CTCL is currently deemed incurable, remission has been achieved for some following allogeneic stem cell transplant (ASCT).[13] Reduced-intensity ASCT may open this therapy to more patients;[9] however, Cowan highlighted an unmet need to find treatments efficacious enough to bring CTCL under sufficient control to undergo ASCT, which necessitates a low tumour burden.

POST-HOC ANALYSIS OF THE MAVORIC TRIAL

Mogamulizumab is a humanised IgG1 κ monoclonal antibody that targets the CCR4 chemokine receptor prevalent on malignant T cells.[14] Cowan was a principal investigator in the international Phase III MAVORIC trial, the largest-ever randomised trial of systemic therapies in CTCL, where significant advantages for relapsed/refractory MF or SS were shown with mogamulizumab (intravenous 1.0 mg/kg weekly for 28 days, then every 2 weeks) in progression-free survival and overall response rate compared to vorinostat (400 mg/day orally).[14]

Recent post-hoc analysis found mogamulizumab was significantly advantageous over vorinostat in those patients with B1 or B2 blood tumour burden for progression-free survival, overall response rate (B2 only), and time to next treatment (Figure 1). Treatment-related treatment-emergent adverse events were less frequent with mogamulizumab and were similar regardless of blood tumour burden.[16]

Analysis of median percentage change in skin response over up to 12 treatment cycles revealed that both mogamulizumab and vorinostat led to progressive decreases.

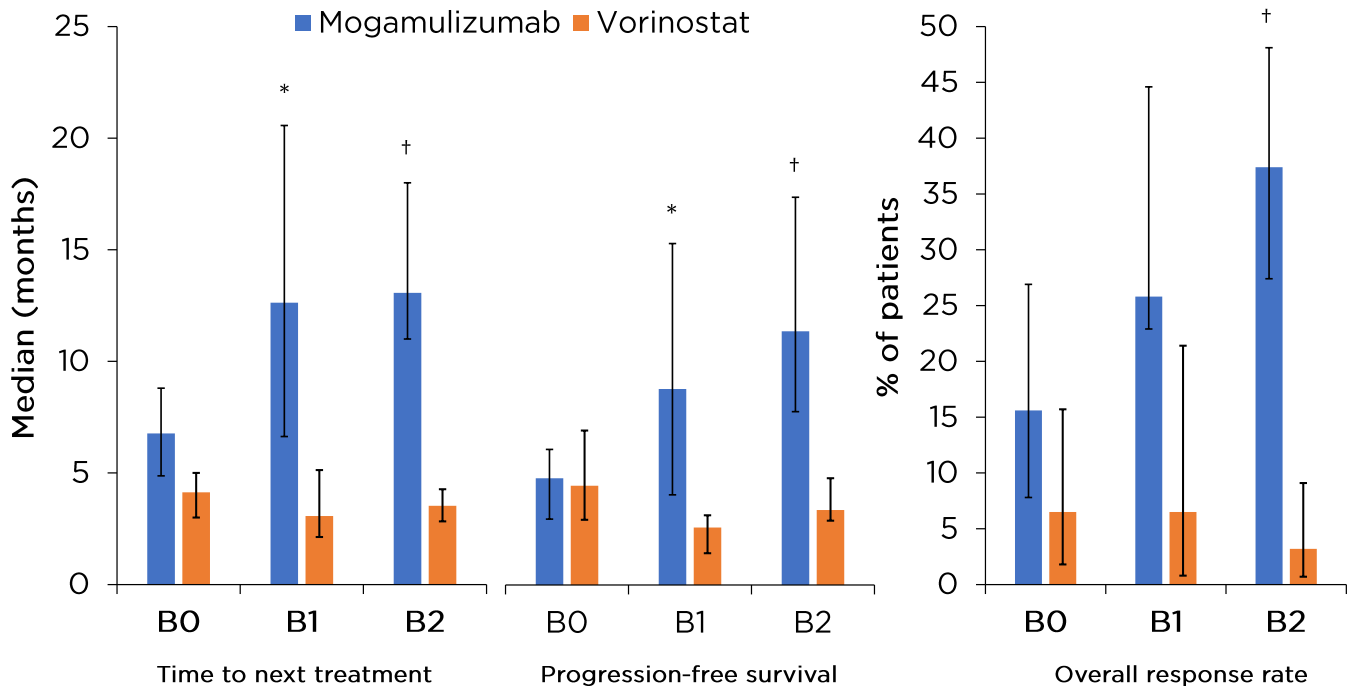

Figure 1: Results of post-hoc analysis of the MAVORIC trial.[16]

*p<0.05.

†p<0.0001.

95% confidence intervals indicated on graphs. Participant numbers for progression-free survival and overall response rate (and time to next treatment): B0: mogamulizumab, n=64 (n=49); vorinostat, n=62 (n=46); B1: mogamulizumab, n=31 (n=25); vorinostat, n=31 (n=18); B2: mogamulizumab, n=91 (n=82); vorinostat, n=93 (n=52).

Notably with mogamulizumab, B1 and B2 groups had the greatest improvements, suggesting a positive correlation between baseline blood involvement and mogamulizumab efficacy in skin.[17]

Similarly, investigation of health-related quality of life factors, including emotional, functional, pruritus, and symptom domains, again showed the largest differences in those with B1 or B2 blood tumour burden, with scores on one measure showing improvements only in this cohort who received mogamulizumab, from Cycle 3 onwards, with a decline in scores for those without blood involvement and those receiving vorinostat (B0, or B1 or B2).[18]

As recurrent haematogenous seeding of lesions has been proposed as one factor possibly driving MF progression,[19] mogamulizumab may be exerting its effects by inhibition of this skin seeding, which could be the mechanism behind why it is particularly advantageous for patients with blood involvement.

MAVORIC notably contained a large number of patients with SS, for whom previously, explained Cowan: "Our ability to change the course of disease has remained frustratingly static." He continued: "Suddenly, there's a drug that has dramatically changed the picture." He discussed that with mogamulizumab "we seem to be seeing an enhanced response in patients who have the most aggressive, poor-prognosis type of disease;" that is, those with the highest blood involvement.

THE UNMET NEEDS OF PEOPLE WITH CTCL

Cowan highlighted how "the great emphasis on future research…is looking at ways in producing agents that have a longer duration of response or finding approaches by which we can maintain the response, be it with milder agents or immune modulation." He also discussed a large unmet need for therapies to be developed that are easier for patients to access (e.g., to address the disruption of visiting a phototherapy centre twice per week for many weeks). Further unmet needs include multi-compartmental efficacy and drug tolerability.

As CTCL is rare, there are little data to determine the treatment impact on early-stage disease. This unmet need is poised to be fulfilled by the PROspective Cutaneous Lymphoma International Prognostic Index (PROCLIPI) study, which involves an international database where patient data are collected in a unified fashion, including clinical, histopathological, and blood details alongside quality-of-life indices.[4] Data are added annually and at every new therapeutic intervention. Cowan explained how, with nearly 1,500 patients already, "we will start to identify prognostic factors that will help guide us into the therapeutic approaches of the future."

Finally, as patient organisations can support patients and families in better understanding CTCL and its management, Cowan discussed the importance of establishing national and international patient support groups, as patients with CTCL may feel especially isolated as "literally nobody's ever heard of their disease."

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Interview

Nikhil Munshi

Professor of Medicine, Harvard Medical School; Associate Director of the Jerome Lipper Multiple Myeloma Center, Dana Farber Cancer Institute, Boston, Massachusetts, USA

NIKHIL Munshi spoke to EMJ about his personal research interests and landmark publications, the impact of the COVID-19 pandemic on multiple myeloma care, and what the future may hold for the care of patients in haematology.

Q1 Following your research fellowship in medical oncology at the Johns Hopkins Oncology Centre, Baltimore, Maryland, USA, what drew you to the combined practice of haematology and oncology?

We are talking about 35 years ago, and some of what drew me to the practice is still true today. There were two major aspects of cancer that were critical: 1) it was an overwhelmingly incurable disease; this has changed over the past 35 years, with many cancers now curable and other treatments improving by the day. But then there was a great need as it was universally a fatal disease. There was a great need for research that improved outcomes. 2) It represents a fascinating area of cellular control. Having an interest in both the biology of disease and biology and normal physiology of cellular changes and genomics, combining the practice of both blood cancers and how to take care of it, became of great interest and importance to me. I would still do the same thing now, 35 years later, because there is still so much more to understand. The research needs and clinical needs became unifying factors for me to practice haematology and oncology as a joint endeavour.

Q2 You are Associate Director of the Jerome Lipper Multiple Myeloma Center at the Dana Farber Cancer Institute, which is currently recognised internationally as one of the top three hospitals specialised in oncology. What do you think other hospitals could learn from the approach taken at Dana Faber?

To summarise the attraction and the strength of Dana Faber I need three words: bench to bedside. I believe what we excel in is outstanding laboratory science: finding new pathways, new molecular and genomic changes, etc. But that's not enough; we need to bring those discoveries to patients and take it from bench to bedside. So that is what

we excel in: finding new approaches that can then be translated into successful treatments, which can lead to curative and improved outcome. Then, there is also the component of going the other way: from bedside to bench. When patients respond we need to find out who responds so that we can do it better, and who does not respond so that we can find those features and improve on them or come up with solutions to overcome resistance mechanisms. Essentially, bringing it back to bench to understand the patient's behaviour and the disease behaviour and improve upon it. That has been the strength and the hallmark of what Dana Faber does: taking successes and treatments to the patient and what counts for the patient. This is the formula that a lot of centres could use to improve upon treatments and therapies.

"To summarise the attraction and the strength of Dana Faber I need three words: bench to bedside. I believe what we excel in is outstanding laboratory science: finding new pathways, new molecular and genomic changes."

Q3 What was the rationale for the establishment of the Myeloma Initiative at Veterans Administration Hospitals and what outcomes have arisen from this?

The veteran population are a unique population; they are outstanding individuals who have served the country, and over the years they have different needs. I have been connected to the veterans hospitals for over two decades and I am very happy and proud to be part of the care of veterans. They deserve the best. Their unique features drove us to establish the initiative and collaborate across all the large veteran hospitals in the USA, to provide them an improved access to care, drugs, and a better understanding of their needs. For example, there is a higher proportion of African American patients who are veterans and there is a higher proportion of veterans who are of older age, who took part in World War II and before that. There is also a need for focused clinical research, which has encouraged us to combine our efforts across the Veterans Administration to learn from each other and develop treatments that are more unique to them.

Q4 Could you outline the key research findings and wider relevance of your recently published policy review article 'Treatment of Relapsed and Refractory Multiple Myeloma: Recommendations from the International Myeloma Working Group'?

What this publication highlights is the success in myeloma so far. There have been 14 new drugs approved in the last 15 years. This has made the treatment of myeloma much better but also more complicated. How do we combine the drugs? What sequence do we use? What dosages do we use? This publication begins to address this. Also, how do we treat relapse and refractory myeloma patients? The initial treatment is more or less standard, with a four-drug regimen, etc. However, later on in treatment we have 10 or more drugs to use and they need to be used appropriately, in the right patient setting, taking into account various features. These features include patient-specific features such as their age, their toxicity, their comorbidities, and their financials, but more importantly their logistical needs and how they have responded to previous treatments. This all needs to be synthesised into how we utilise these drugs. This particular publication combines these aspects. The problems we have are problems of success; however, we need to realise that there is still more work to do. Patients do relapse, even after taking the drugs available, so we need to find new treatments and new approaches that can be utilised more appropriately. The most recently approved agent is a chimeric antigen receptor T cell (CAR T), which is completely opening new doors for treatment of myeloma.

Q5 You currently have more than 400 peer-reviewed publications and book chapters to your name, primarily for your research in multiple myeloma. What do you believe to be the current gaps in literature and what topics warrant greater attention?

We have incredible access to technology compared to what we used to have. A whole-genome sequence can be done in less than a week and we can have all the data about the genome. However, we still have big gaps in our knowledge about what causes myeloma, what causes the progression of early-stage monoclonal gammopathy of undetermined significance and smouldering myeloma to myeloma. What are the features causing the progression? The genomic changes that are taking place is because of the genomic instability; that is what causes myeloma to become resistant. We need to understand the mechanisms that might be helping the cancer to continue growing. And then more important are the resistance mechanisms and the immune changes, which are important because the immune system, as we are beginning to understand, has such a tremendous ability for impact and we need to learn how to harness that. So there are a number of gaps in our knowledge about how cancer cells grow and how the micro-environment supports this growth. There is the old 'seed versus soil' theory: cancer is the seed, but it needs the right soil to grow. We need to understand and target both to optimally control the disease. I think that is the gap that are we are beginning to understand, but we have a lot more to do to make it a very curable disease. I believe we have taken the ultimate steps to reaching this goal.

"That initial international effort taught us a lot about how to do an international study but also how to overcome a threat like COVID-19 in patients with an immunosuppressed disease."

Q6 A major focus of your laboratory is the development of immunotherapeutic agents, such as chimeric antigen

receptor-engineered T cell therapies, to target the evasion tactics of multiple myeloma. Could you tell us how this works and summarise the current stage of the research into immunotherapy and immuno-gene therapy?

My laboratory has been focused on understanding the immune changes in myeloma and developing immune-based treatments for the last 30 years. The most-recently approved CAR T agent, the first truly immune-directed treatment, is the BCAM (B-cell maturation antigen)-directed CAR T cell immunotherapy for myeloma and is the first to become commercially available to patients. What is more, the results of this study and similar studies are so incredibly exciting that they have opened up a totally new possibility for the prognosis of this cancer. I think I would call this a last step to curing this disease. What is done here is that we use the power of the immune cells to get rid of what is not needed in or foreign to the body. We take the immune cells and genetically modify them to introduce certain features that allow the immune cells to identify specifically the cancer cells, nothing else. This allows the immune cells to bind to or come close to the cancer cells and, in the process, immune cells identify the cancer cells and kill them. In that process, the immune cells divide and expand further to become stronger and kill more cancer cells. So, we give these features to the immune cells and they do what we expect and hope they will do, which is to kill cancer cells in large number. And there are many more similar drugs coming out. They work in patients who are on six different lines, on average, of treatment. Where we traditionally would expect no treatment to give more than a 20% response rate or so, which would last for 2–3 months, this treatment now gives us an 80–90% response rate that last for 12 months and beyond. So, it is incredibly effective as the last treatment where nothing else is possible. Now we are beginning to introduce it in the earlier stages where we expect the responses to be even greater and the durability, hopefully, even longer. And when we witness a subgroup of patients who do not eventually relapse, it will be a population that we can save and possibly cure using this treatment. We are not ready to say that yet, but I think the treatment has the potential to get us there.

Q7 In October 2020, you co-authored a paper evaluating the impacts of the COVID-19 pandemic on the management and treatment of multiple myeloma. Could you explain the pivotal messages of this study?

There are many messages from this study. Firstly, this particular study was truly an international effort. Investigators from many countries in North and South America, Europe, and Asia participated to give their data very acutely, in one effort. Everybody joined hands to understand what COVID-19 does to patients with myeloma. Secondly, it was early days and we did not have a vaccination and we did not understand the disease as well as we do today. But it told us that patients with myeloma have a specific susceptibility to a more severe form of COVID-19 and there was a high mortality in the early days in these patients. This has now changed with the vaccine roll-out and other things. But there was something else: it told us that immunosuppression, which we observe in myeloma, is part of the immune problem. It plays a critically important role in controlling COVID-19. Therefore, we eventually came up with some guidelines that we shouldn't not treat patients with myeloma because of COVID-19, which was the initial knee-jerk reaction. In fact, the point we came out with was that we actually needed to treat myeloma effectively so that the immune system would become better and thereby there would be fewer issues with COVID-19. And finally, it became clear over time from that publication that patients with myeloma, by not having normal immune systems, may or may not have an adequate immune response to the vaccine and that we still need to be careful. We need to measure the vaccine responses and manage patients with myeloma in a very specific way to make them safe from the current pandemic. That initial international effort taught us a lot about how to do an international study but also how to overcome a threat like COVID-19 in patients with an immunosuppressed disease.

Q8 You have expressed the importance of optimally defining risk in multiple myeloma. Could you highlight the potential benefits of revising the current definition, especially in relation to the treatment received by patients?

Over the years we have defined high-risk myeloma and those patients with myeloma who may not have such a good outcome, and then we have gone after those features to try to overcome it. So every year we find a high-risk disease and develop new treatments, which can better treat high-risk patients with those high-risk features. And by that we then identify patients with a new, high-risk feature. So, the treatments can overcome the risk in a setting where new features appear. I think risks are dynamic, not because they change, but because our treatments change, and so with each new treatment that we develop, we have to redefine what the risk is. This has happened for the past 30 years. There was a time when chromosome 13 deletion was a risk for myeloma; today we do not even care for it because all current treatment can overcome this. There was time when t(4;14) myeloma was considered a very high-risk myeloma; now the treatments we use can overcome the high risk in those patient populations. We have our current risk stratification: 17p deletion is not good myeloma at the moment, along with a few others, and we are developing treatments to overcome this. So, I think we have to remember that with changing treatments, risk features are dynamic, and we have to evolve with the treatment evolution to identify patients who do not have as good an outcome and specially treat them to overcome those features.

Q9 Are there any innovations on the horizon in the field of multiple myeloma treatment that you think are particularly noteworthy, and what barriers to progression still need to be overcome?

One of the new understandings in myeloma is the minimal residual disease (MRD) that we and others have worked on. MRD is a situation where we are able to identify 1 myeloma cell in a million cells, which is 10,000-fold better than what we do today, or what we did yesterday. Getting patients to a state of MRD negativity and developing treatments for that is our goal. This is also going to identify a successful treatment much more quickly as it gets accepted as a surrogate for the current survival outcomes. There are many treatments in the pipeline that are exceedingly exciting and have great potential; a lot of them are immune-based, and besides the CAR T cells, we have bispecific antibodies and immune response modifiers. We have newer agents and newer targets that can affect protein catabolism. Then, we have targeted treatments for various myeloma subgroups and these are all very exciting, especially the immune-based methods. Combined with the newer methods of measuring myeloma, MRD and the others will ultimately give us the best outcome for these patients

Q10 Since your appointment as President of the International Myeloma Society (IMS), what has been your proudest achievement?

I think what has been the most gratifying so far is the society's ability to fund research for multiple myeloma. We have two efforts that I am very proud of and I think will make a big difference. One is the 'Career Development Award', which is specially devised to support the careers of young investigators, the 'new blood' that can be fostered that will be the future of myeloma research. Second, with great philanthropic support from the Paula and Rohger Riney Foundation, we have launched the 'Translational Research Award', which gives significant funding to myeloma research to develop translational efforts to bring about drugs that can directly benefit new drugs and new treatments, which can benefit patients with myeloma directly. Truly translational research and not just laboratory research. And this is also directed at attracting investigators from other cancer fields to use their success in lymphoma or leukaemia and apply that to myeloma and enrich the efforts that we have. So, we have funded both these efforts this year and we plan to do this for long period of time. The society has become one of the largest funders of myeloma research. I am very proud of these accomplishments of the society. ■

Von Willebrand Factor and ADAMTS13 in COVID-19 and Beyond: A Question of Balance

EDITOR'S PICK

My choice for the Editor's Pick this issue could not fail to go to this review article by Favaloro et al., who analyse the relationship between von Willebrand factor and ADAMTS13 in the syndrome that accompanies SARS-CoV-2 infection. This article is important, not only because it is so dramatically up-to-date, but also because it helps to clarify what was unclear for long months in spring last year. This detailed review demonstrates once again that the human body is based on a delicate balance of activations and inhibitions.

Dr Emanuele Angelucci

Chair, Hematology and Transplant Unit, Ospedale Policlinico San Martino; Transplant Program Director, Istituto di Ricovero e Cura a Carattere Scientifico (IRCCS), Genova, Italy.

Authors: *Emmanuel J Favaloro,[1,2] Brandon Michael Henry,[3] Giuseppe Lippi[4]

1. Haematology, Sydney Centres for Thrombosis and Haemostasis, Institute of Clinical Pathology and Medical Research (ICPMR), NSW Health Pathology, Westmead Hospital, Sydney, Australia
2. School of Biomedical Sciences, Charles Sturt University, Wagga Wagga, Australia
3. Cardiac Intensive Care Unit, The Heart Institute, Cincinnati Children's Hospital Medical Center, Ohio, USA
4. Section of Clinical Biochemistry, University of Verona, Verona, Italy

*Correspondence to emmanuel.favaloro@health.nsw.gov.au

Disclosure: The authors have declared no conflicts of interest.

Received: 08.02.21

Accepted: 16.03.21

Keywords: ADAMTS13, COVID-19, secondary thrombotic microangiopathy, thrombotic thrombocytopenic purpura (TTP), von Willebrand factor (VWF).

Citation: EMJ Hematol. 2021;9[1]:55-68.

Abstract

von Willebrand factor (VWF) is a large, adhesive, multimeric protein involved in haemostasis. The larger the size (or number of VWF multimers), the greater the functionality of the protein. A deficiency or defect in VWF can lead to von Willebrand disease (VWD) and cause bleeding, whereas an increase in VWF may cause thrombosis. ADAMTS13 (a disintegrin and metalloproteinase with a thrombospondin type 1 motif, member 13), sometimes called VWF-cleaving protease, is primarily responsible for controlling the size of VWF. Although a deficiency of ADAMTS13 may be caused by many factors, the most severe deficiency (<10% of normal levels) arises in thrombotic thrombocytopenic purpura, which is characterised by the presence of ultra-large VWF and resulting thrombosis. The relative levels of both VWF and ADAMTS13 can be described by either the VWF/ADAMTS13 ratio or the ADAMTS13/VWF ratio, depending on author preference. Typically, this reflects VWF antigen levels and ADAMTS13 activity. The normal ratio, where both VWF and ADAMTS13 are in balance, is close to unity (or 1.0). In VWD, the VWF/ADAMTS13 ratio approaches zero, whereas in thrombotic thrombocytopenic purpura the ADAMTS13/VWF ratio approaches zero. Recent evidence has emerged that COVID-19, which may

be accompanied by high prothrombotic risk, could be characterised in some patients as expressing an imbalance of VWF and ADAMTS13, or a high VWF/ADAMTS13 ratio, in a clinical picture resembling a secondary thrombotic microangiopathy. The current narrative review discusses the so-called VWF/ADAMTS13 axis in COVID-19 and beyond.

INTRODUCTION

von Willebrand factor (VWF) is a large, adhesive, multimeric protein involved in haemostasis. The larger the size (or number of VWF multimers), the greater the functionality of the protein.[1] A deficiency or defect in VWF can lead to von Willebrand disease (VWD) and cause bleeding.[2] Deficiency infers a relative lack of VWF protein, whereas defect infers a dysfunctional protein.

Of more relevance to this review is that an increase in VWF may cause thrombosis.[3] Although VWF increase per se may be associated with thrombosis, it is the increase in the larger VWF protein moieties (sometimes called high-molecular-weight [HMW] VWF) that are more likely to lead to thrombosis. Another protein, ADAMTS13 (a disintegrin and metalloproteinase with a thrombospondin type 1 motif, member 13), is primarily responsible for controlling the size of plasma VWF. ADAMTS13 achieves this by proteolytic cleavage of VWF multimers and is hence sometimes called von Willebrand factor-cleaving protease.[4] This knowledge developed from the pioneering work of Moake et al.[5] in 1982 and Furlan et al.[6] and Tsai et al.[7] in 1996.

A deficiency of ADAMTS13 may be caused by many factors. Notably, the most severe deficiency of ADAMTS13 arises in thrombotic thrombocytopenic purpura (TTP).[4] In addition to characteristic features, including low platelet count, microangiopathic haemolytic anaemia, and increased lactate dehydrogenase, the disorder is characterised by levels of ADAMTS13 <10% of normal, with consequent presence of ultra-large VWF; accordingly, thrombosis is a key feature of TTP.[4]

The relationship between VWF and ADAMTS13 is sometimes called the VWF/ADAMTS13 axis. The relative levels of both VWF and ADAMTS13 in the normal state can be described as a percentage of normal or in U/dL, which for both would average approximately 100%. The relative level or relationship can also be described by using either the VWF/ADAMTS13 ratio or the ADAMTS13/VWF ratio, depending on an author's preference. In general, the VWF level usually used is that measured by its antigen, and the level of ADAMTS13 usually used is that measured by its activity; however, sometimes VWF activity and ADAMTS13 antigen may be used instead. Why some authors use VWF/ADAMTS13 and others ADAMTS13/VWF may relate to their main interest; those with primary interest in VWF may favour the VWF/ADAMTS13 ratio, whereas those with primary interest in ADAMTS13 may favour the ADAMTS13/VWF ratio. Preference may also relate to pragmatism. In this review, the authors use the VWF/ADAMTS13 ratio because it is the excess of VWF that essentially drives the pathophysiology of thrombosis. The normal ratio, where both VWF and ADAMTS13 are in balance, is close to unity (1.0) but may range from approximately 0.5–2.0. In either case, haemostasis related to the VWF/ADAMTS13 axis is normal or in balance (Figure 1A).

In VWD, the VWF/ADAMTS13 ratio approaches zero. Use of the alternate ADAMTS13/VWF ratio can lead to huge numbers, or even attempted numerical division by zero in severe Type 3 VWD, and therefore approaches infinity. In contrast, in thrombotic microangiopathies the ADAMTS13/VWF ratio approaches zero; alternate use of the VWF/ADAMTS13 ratio can lead to huge numbers, or even attempted division by zero in TTP, the most severe microangiopathy, and thus approaches infinity. In either case (i.e., for VWD or TTP), neither ratio (VWF/ADAMTS13 or ADAMTS13/VWF) is usually reported for reasons explained below. In the authors' view, this is appropriate. Nevertheless, the ratio between VWF and ADAMTS13 has been shown to be of clinical significance in several pathological conditions; for example, as a predictor of outcome in acute ischaemic brain injury,[8] predicting thrombotic complications in cirrhosis and post-hepatectomy,[9,10] and prognostication after myocardial infarction.[11]

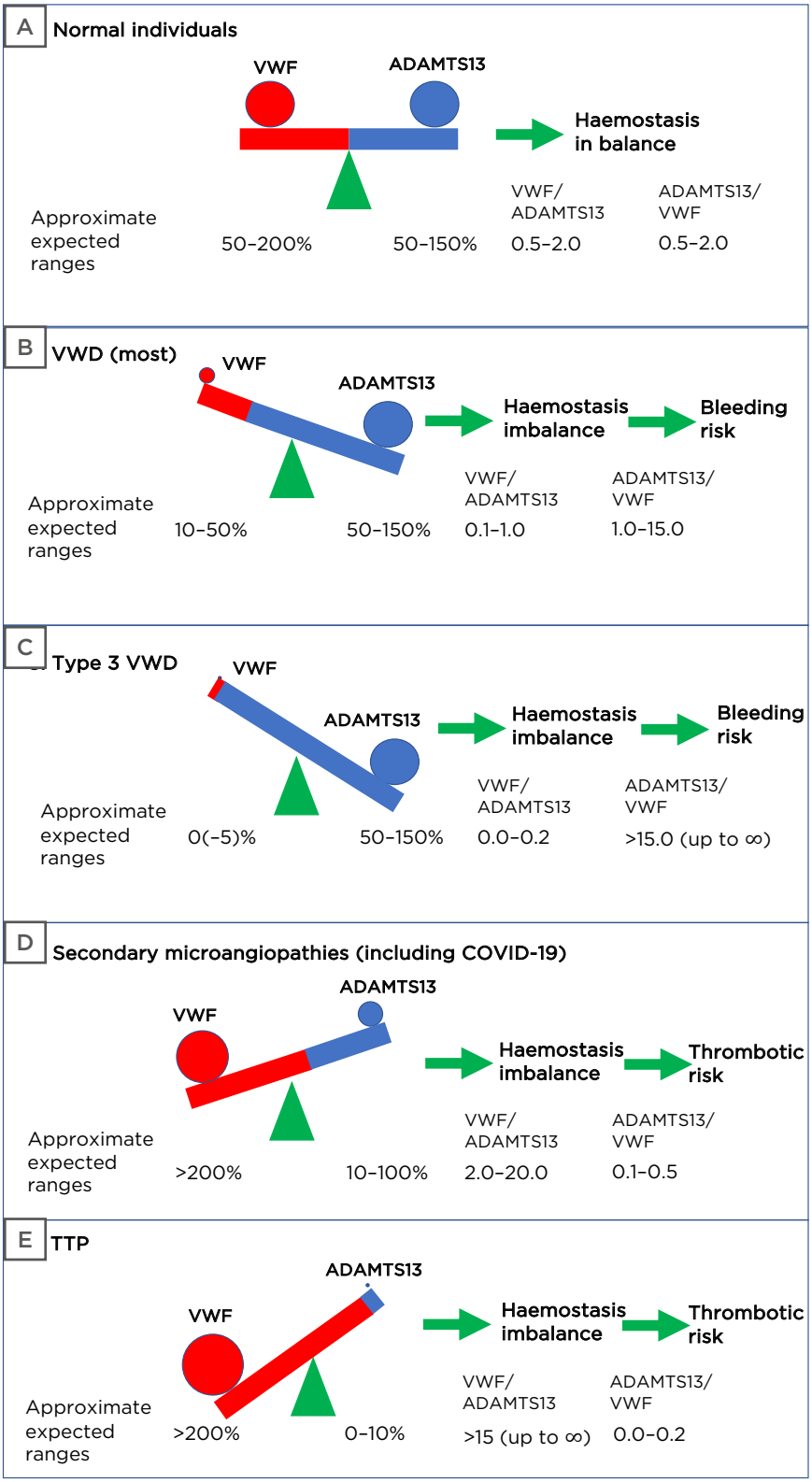

Figure 1: The VWF/ADAMTS13 axis in A) normal individuals; B and C) VWD; and D and E) microangiopathies.

COVID-19 may present as a **D**) secondary thrombotic microangiopathy. The stated values of VWF, ADAMTS13, and their ratios are approximate only. Values differ according to VWF and ADAMTS13 test methods, and according to patient status.

ADAMTS13: a disintegrin and metalloproteinase with a thrombospondin type 1 motif, member 13; VWD: von Willebrand disease; VWF: von Willebrand factor; TTP: thrombotic thrombocytopenic purpura.

More relevant for this review is that recent evidence has emerged suggesting COVID-19, which is often associated with a high prothrombotic risk,[12-15] may be characterised in some patients as an imbalance of VWF and ADAMTS13, or a high VWF/ADAMTS13 ratio, in a clinical picture closely resembling a secondary thrombotic microangiopathy. The current narrative review discusses the so-called VWF/ADAMTS13 axis in COVID-19 and beyond. The authors also advocate for increased use of VWF/ADAMTS13 reporting in a wide variety of pathological conditions involving their dysregulation.

VON WILLEBRAND FACTOR AND DISEASE

As mentioned, VWD is characterised by low levels of or defective VWF;[2] this causes bleeding. In these patients, the focus is on VWF because this represents the abnormal event.

There are three main types of VWD. Types 1 and 3 represent partial and total deficiencies in VWF, respectively, and Type 2 comprises four separate subtypes: 2A, which represents selective deficiency in HMW VWF; 2B, which represents a hyperfunctional form of VWF, the consequence of which is also deficiency in HMW VWF; 2N, which represents a relative defect in VWF binding to factor VIII, the consequence of which is reduced plasma levels of factor VIII; and 2M, which represents a relative defect in VWF not characterised by the other types (Table 1).[2,16] Of interest, the clinical severity of VWD is not always proportional to the level of VWF but in general, the lower the level of VWF activity, the greater the bleeding risk.[2]

In theory, ADAMTS13 levels should be normal in VWD but are not generally assessed. This is entirely appropriate because the pathological state is bleeding caused by a lack of or dysfunctional VWF. Consequently, there is no anticipated change in ADAMTS13 level or activity. Thus, clinicians may see results related to VWF level (antigen; VWF:Ag) and function (e.g., platelet binding or collagen binding) as relevant but not results related to ADAMTS13.[2,16] Thus, neither VWF/ADAMTS13 nor ADAMTS13/VWF ratios are ever reported in VWD. This is of course appropriate. However, should the VWF/ADAMTS13 axis be considered this could be determined to be in an imbalanced state because of the reduction in either VWF level or activity (Figures 1B and C).

Of additional interest is that Type 2A VWD may arise from either decreased production of HMW VWF caused by faulty assembly of HMW multimers or increased clearance of HMW VWF by ADAMTS13 as a result of structural changes in VWF, making this dysfunctional VWF more susceptible to cleavage by ADAMTS13.

ADAMTS13 IN THROMBOTIC THROMBOCYTOPENIC PURPURA AND OTHER THROMBOTIC MICROANGIOPATHIES

As mentioned, TTP is characterised by the deficiency of ADAMTS13, typically <10% of normal activity.[4]

Table 1: Types of von Willebrand disease.*

Characteristic features	VWF indices (approximate values)	Approximate incidence, inheritance	ADAMTS13 link
Type 1 VWD			
Loss of VWF but VWF present is functionally normal	VWF:Ag: 5–30% VWF:RCo:† 5–30% VWF:CB: 5–30% RCo/Ag ratio: >0.6 CB/Ag ratio: >0.6	60–70% of all VWD, (usually) autosomal dominant	ADAMTS13 levels expected to be normal. Thus, ADAMTS13/VWF ratio would be high and VWF/ADAMTS13 ratio would be low.

Table 1 continued.

Characteristic features	VWF indices (approximate values)	Approximate incidence, inheritance	ADAMTS13 link
Type 2A VWD			
Loss of HMW VWF. Thus, VWF present is functionally defective. Usually, absolute level of VWF also low	VWF:Ag: 5–50% RCo/Ag ratio: <0.6 CB/Ag ratio: <0.6	~40% of all Type 2 VWD or ~10% of all VWD, (usually) autosomal dominant	Two types of 2A VWD: increased susceptibility of VWF to ADAMTS13 cleavage or faulty production of VWF multimers. In either case, ADAMTS13 levels expected to be normal. Thus, ADAMTS13/VWF ratio would be high and VWF/ADAMTS13 ratio would be low.
Type 2B VWD			
Increased VWF adhesive function, leading to loss of HMW VWF. Thus, VWF present is functionally defective. Absolute level of VWF may be normal or low	VWF:Ag: 10–100% RCo/Ag ratio: <0.6 CB/Ag ratio: <0.6	~10% of all Type 2 VWD or <5% of all VWD, autosomal dominant	ADAMTS13 levels expected to be normal. Thus, ADAMTS13/VWF ratio and VWF/ADAMTS13 ratio would be dependent on level of VWF.
Type 2N VWD‡			
Loss of VWF factor VIII binding. Absolute level of VWF may be normal or low depending on whether patient is heterozygous or homozygous/double heterozygous for the defect	VWF:Ag: 10–100% RCo/Ag ratio: >0.6 CB/Ag ratio: >0.6	~10% of all Type 2 VWD or <5% of all VWD, autosomal recessive	ADAMTS13 levels expected to be normal. Thus, ADAMTS13/VWF ratio and VWF/ADAMTS13 ratio would be dependent on level of VWF.
Type 2M VWD§			
Other VWF dysfunction not characterised within the other Type 2 VWD groups. Absolute level of VWF may be normal or low	VWF:Ag: 5–50% RCo/Ag ratio: <0.6 and/or CB/Ag ratio: <0.6	~40% of all Type 2 VWD or ~10% of all VWD, autosomal dominant	ADAMTS13 levels expected to be normal. Thus, ADAMTS13/VWF ratio and VWF/ADAMTS13 ratio would be dependent on level of VWF.
Type 3 VWD			
Absence of VWF	VWF:Ag: 0(–5)% VWF:RCo:† <5% VWF:CB: <5%	<5% of all VWD, autosomal recessive	ADAMTS13 levels expected to be normal. Thus, ADAMTS13/VWF ratio would be infinity and VWF/ADAMTS13 ratio would be zero.

*ADAMTS13 levels would be expected to be normal in patients with VWD; however, ADAMTS13 levels are not normally assessed in these patients. This is because the important findings relate to levels and function of VWF. Loss of VWF or VWF function represents a risk factor for bleeding.

†VWF:RCo represents an original platelet GPIb binding assay that uses ristocetin and platelets to assess VWF activity. More recent variants of GPIb binding are VWF:GPIbR and VWF:GPIbM. In general, VWF:RCo, VWF:GPIbR, and VWF:GPIbM are similar in that they all assess platelet GPIb binding activity.[16]

‡Type 2N VWD requires other assays for diagnosis.

§Type 2M VWD may express abnormal glycoprotein Ib binding and/or collagen binding.

ADAMTS13: a disintegrin and metalloproteinase with a thrombospondin type 1 motif, member 13; Ag: antigen; CB: collagen binding; GPIb: glycoprotein Ib; HMW VWF: high-molecular-weight von Willebrand factor; RCo: ristocetin cofactor; VWD: von Willebrand disease; VWF: von Willebrand factor; VWF:Ag: von Willebrand factor antigen; VWF:CB: von Willebrand factor collagen binding; VWF:RCo: von Willebrand factor ristocetin cofactor.

A functional or quantitative deficiency in ADAMTS13 can lead to microvascular thrombosis because of accumulation of ultra-large VWF multimers, which would normally be cleaved by ADAMTS13 into smaller, less active forms to inhibit thrombosis and maintain normal haemostasis. TTP can be congenital (caused by genetic mutations) or acquired (arising from the presence of inhibitors), both resulting in microvascular thrombosis and subsequent microangiopathic haemolytic anaemia.[17] The diagnostic detection of an inhibitory autoantibody (usually IgG) against the spacer domain of the protease is key to differentiating congenital from acquired TTP.[17]

In patients with TTP, the focus may be on both ADAMTS13 and VWF because both may represent an abnormal event, with abnormally low ADAMTS13 activity leading to abnormally high levels of ultra-large VWF.

Nevertheless, only ADAMTS13 levels are typically measured in TTP; HMW VWF levels are assumed to be high and a feature of the pathophysiology, and are thus rarely quantified. Again, neither VWF/ADAMTS13 nor ADAMTS13/VWF ratios are generally reported in TTP. The authors believe this to be appropriate for TTP, which represents an extreme version of thrombotic microangiopathy. However, should the VWF/ADAMTS13 axis be considered this could be determined to be in an imbalanced state (Figures 1D and E) and in the opposite direction to VWD.

While the extreme deficit of ADAMTS13 activity (<10%) is pathognomonic for TTP, substantial decreases in ADAMTS13 activity have also been observed in several other thrombotic microangiopathies. Mild decreases or impairment of ADAMTS13 activity can be observed in some cases of Shiga toxin-producing *Escherichia coli*-associated haemolytic uremic syndrome, in which the toxin can inactivate ADAMTS13 and propagate thrombosis,[18] as well as atypical haemolytic uremic syndrome, usually driven by genetically predisposed overactivation of the complement system.[19] Moreover, decreased ADAMTS13 can be observed in sepsis, contributing to the septic coagulopathy and associated with poor prognosis.[20] Decreases in ADAMTS13 have also been reported in patients with malignant hypertension, solid organ transplantation, malignancy, and autoimmune diseases.[21]

COVID-19, VON WILLEBRAND FACTOR, AND ADAMTS13

COVID-19 is caused by viral infection with the severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2). The predominant pathophysiological features of severe COVID-19 often reported include respiratory distress and hypoxia, further developing into severe acute respiratory syndrome (SARS), interstitial pneumonia, acute respiratory distress syndrome (ARDS), and finally multi-organ injury.[12] Lung involvement largely stems from high expression of angiotensin-converting enzyme 2 receptors (ACE2R) on endothelial cells, which constitute almost one-third of the cells in the alveolar component of the lungs.[13] ACE2R constitute a binding site for SARS-CoV-2 and probably the main entry point for viral invasion. In the lungs, this leads to endothelial cell activation followed by an inflammatory–thrombotic process and an associated coagulopathy.[12] However, it is now also clear that both localised microthrombosis and peripheral or systemic thrombosis may develop. Thus, both pulmonary thrombosis and pulmonary embolism (PE) can occur, along with micro- and macrothrombosis in other organs (e.g., heart, kidney, liver, and spleen).[14] Essentially, any tissue or organ containing endothelium or otherwise expressing significant numbers of ACE2R can be the target of COVID-19-associated coagulopathy. Indeed, COVID-19 affects all facets of haemostasis, including endothelium, platelets, coagulation, and fibrinolysis.[12-15,22,23] COVID-19 can therefore cause a variety of pathologies depending on which organ is damaged, especially cardiac damage and acute kidney injury (AKI). Similarly, it may be difficult to tease out microthrombosis in these patients, which is typically only seen on post-mortem analysis.[24]

Of particular relevance to the current review is that several reports have now identified increased levels of VWF and/or decreased levels of ADAMTS13 to be associated with COVID-19 and the severity of COVID-19 or associated multi-organ injury (Table 2).[25-60] In this regard, COVID-19 may represent a clinical picture similar to a secondary thrombotic microangiopathy (Figure 1D).

Table 2: Summary of literature related to VWF and ADAMTS13 in COVID-19.

Study	Main findings	VWF:Ag, ADAMTS13 levels in COVID-19	Link to COVID-19 severity
(Raised) VWF			
Panigada et al.,[25] 2020	Raised VWF in 11/11 patients with COVID-19 in ICU	VWF:Ag: 529 (210–863)*	Only in so far as all patients in ICU
Poissy et al.,[26] 2020	107 first consecutive patients with confirmed COVID-19 admitted to ICU for pneumonia	Not reported	VWF associated with a greater PE risk
Helms et al.,[27] 2020	Raised VWF in 150 patients with COVID-19 admitted to ICU for ARDS	VWF:Ag: 455 (350–521)†	Only in so far as all patients were in ICU with ARDS
Goshua et al.,[28] 2020	68 patients with COVID-19 (48 ICU and 20 non-ICU) plus 13 non-hospitalised, asymptomatic controls. VWF raised in both COVID-19 groups but higher in patients admitted to ICU	VWF:Ag: 565 (199)‡	Mortality was significantly correlated with VWF
Ladikou et al.,[29] 2020	24 consecutive severely ill patients testing positive for COVID-19 (ICU or high-acuity ward). VWF highly elevated and significantly higher in those who died. Reduced ADAMTS13 measured in 1 patient with massive DVT and PE and very high VWF	VWF:Ag: 350 (302–433)†	VWF significantly higher in those who died compared to survivors
Masi et al.,[30] 2020	28 consecutive patients with severe ARDS in ICU: 17 patients with COVID-19 versus 11 patients with ARDS without COVID-19. VWF raised in both cohorts but did not differ between ARDS cohorts	VWF:Ag: 444 (338–520)†	Only in so far as all patients had severe ARDS
Sardu et al.,[31] 2020	164 patients with hypertension and COVID-19. Raised VWF with higher levels in non-O blood group than O group and in those with higher rates of cardiac injury and death	VWF:Ag: 239 (115–476)†	VWF was an independent predictor of both cardiac injury and deaths in patients with hypertension and COVID-19
Rauch et al.,[32] 2020	243 adult patients with COVID-19 admitted to hospital. VWF levels were associated with adverse outcomes (increased oxygen requirements, thrombosis, and death at Day 30) and highest for patients directly admitted to the ICU	VWF:Ag: 361 (128)‡	Higher VWF in sickest patients
Hoechter et al.,[33] 2020	22 patients with COVID-19 and ARDS versus 14 with another infection (bacterial or viral) pneumonia (control group) with ARDS. VWF high in 7 patients tested for COVID-19	VWF:Ag: 300 (249–371)†	Not evaluated
Taus et al.,[34] 2020	VWF higher in patients with COVID-19 (n=10) than healthy controls (n=20)	VWF:Ag: 280.8 (73.1)‡	Not reported
Fan et al.,[35] 2020	12 patients admitted to ICU with severe COVID-19 who were on either mechanical ventilation or on high-flow oxygen. All had elevated VWF	VWF:Ag: 320 (259–371)	Only in so far as all patients had severe COVID-19
Cugno et al.,[36] 2020	148 patients with COVID-19 of different severity. Patients had high plasma levels of VWF, which paralleled disease severity	VWF:Ag: 395 (251–667)† (severe COVID-19)	Levels of VWF increased with severity of COVID-19

Table 2 continued.

Study	Main findings	VWF:Ag, ADAMTS13 levels in COVID-19	Link to COVID-19 severity
Ward et al.,[37] 2020	28 patients with COVID-19 admitted to ICU. Markedly increased plasma VWF:Ag in patients with severe COVID-19	VWF:Ag: 365 (270–568)†	VWF levels high in patients admitted to ICU with COVID-19 but no difference between VTE/death versus non-VTE/survivor groups
Ruberto et al.,[38] 2021	19 patients with COVID-19 versus 10 healthy volunteers. VWF elevated in patients with COVID-19	VWF:Ag: 331 (105)‡	Not evaluated
Heinz et al.,[39] 2021	27 patients with COVID-19. VWF elevated in all patients with COVID-19	VWF:Ag: 554 (431–600)†	Not evaluated
Philippe et al.,[40] 2021	208 patients with COVID-19. Elevated VWF, which scaled according to clinical severity	VWF:Ag: 507 (428–596)† (critical COVID-19)	VWF scaled according to clinical severity
Vassiliou et al.,[41] 2021	38 critically ill patients admitted to ICU with COVID-19: 28 survivors and 10 non-survivors, with highest VWF in non-survivors	VWF:Ag reported in ng/mL	VWF higher in non-survivors than survivors
(Lowered) ADAMTS13			
Martinelli et al.,[42] 2020	Mild reduction of ADAMTS13 activity in 13 patients with COVID-19 hospitalised for interstitial pneumonia	ADAMTS13: 47 (40–55)†	Not evaluated
Rovas et al.,[43] 2020	23 hospitalised adult patients with moderate-to-severe or critical COVID-19. ADAMTS13 decreased significantly with increasing COVID-19 severity and also associated with 60-day mortality	ADAMTS13 reported in arbitrary units	ADAMTS13 decreased with increasing COVID-19 severity and associated with 60-day mortality
Alharthy et al.,[44] 2020	3 patients with COVID-19	All had ADAMTS13 ≤15%	Not evaluated
(Raised) VWF and (lowered) ADAMTS13			
Huisman et al.,[45] 2020	Lowered ADAMTS13, raised VWF, and raised VWF/ADAMTS13 ratio in 12 patients admitted to ICU with a clinical suspicion of microangiopathy in severe COVID-19	VWF: 408 (90)‡ ADAMTS13: not reported VWF/ADAMTS13: 8.5 (6.7)‡	Only in so far as all patients were in ICU/required ventilator use
Escher et al.,[46] 2020	High VWF in 3/3 severely ill patients with COVID-19. All 3 had normal ADAMTS13 levels	VWF: 555, 329, 396 ADAMTS13: 56, 83, 81	Only in so far as all patients had severe COVID-19
Bazzan et al.,[47] 2020	88 consecutive patients with COVID-19 admitted. ADAMTS13 reduced and VWF raised	VWF: 396 (113)‡ ADAMTS13: 32 (16)‡ (non-survivors COVID-19)	Patients who died had lower levels of ADAMTS13 and higher levels of VWF when compared to those with non-fatal outcomes
Morici et al.,[48] 2020	VWF increased in 6/6 and ADAMTS13 reduced in 5/6 patients with COVID-19 in ICU	VWF: 772, 735, 568, 455, 763, 511 ADAMTS13: 24, 37, 30, 56, 44, 33	Only in so far as all patients had severe COVID-19

Table 2 continued.

Study	Main findings	VWF:Ag, ADAMTS13 levels in COVID-19	Link to COVID-19 severity
Blasi et al.,[49] 2020	23 patients with COVID-19. High VWF and low ADAMTS13	VWF: 306 (200-421)† ADAMTS13: 47 (26-66)† (2 patients <10%)	VWF higher in patients with severe COVID-19. ADAMTS13 reduced in both cohorts and not significantly different
Fraser et al.,[50] 2020	10 patients with COVID-19 compared with healthy control subjects. Patients who tested positive for COVID-19 had raised plasma VWF. No reduction observed in ADAMTS13	VWF: reported as ng/mL ADAMTS13: not reported	Not evaluated
Sweeney et al.,[51] 2020	181 hospitalised patients with COVID-19. Patients who died had significantly lower ADAMTS13 activity and significantly higher VWF levels compared to patients discharged. Only 30% of patients with an initial ADAMTS13 activity <43% survived versus 60% with ADAMTS13 ≥43% who survived. The number of patients that required ventilation with an initial ADAMTS13 <43% was more than twice that of patients with initial ADAMTS13 >43%	VWF: 441 (308–598)† ADAMTS13: 49 (36–65)† (non-survivors COVID-19)	Non-survivors had significantly lower ADAMTS13 activity levels and higher VWF. Patients with thrombosis exhibited significantly higher VWF activity
Hardy et al.,[52] 2020	21 patients admitted to ICU with COVID-19. VWF elevated and ADAMTS13 activity reduced	VWF: 438 (357–534)† ADAMTS13: 61 (40–65)†	Not evaluated
Mancini et al.,[53] 2020	50 patients with COVID-19 stratified according to admission to three different intensities of care units: low, intermediate, and high. VWF levels were markedly elevated in patients with COVID-19 and increased with intensity of care. Conversely, ADAMTS13 activity levels progressively decreased with increasing intensity of care	VWF: 476 (380–537)† ADAMTS13: 55 (42–68)† (high COVID-19 group)	Significant alteration of the VWF/ADAMTS13 axis in patients with COVID-19, with an elevated VWF/ADAMTS13 ratio that strongly associated with disease severity
Henry et al.,[54] 2020	52 adult patients with COVID-19 stratified by presence of AKI. Overall, 23% had a relative deficiency in ADAMTS13, while 81% had elevated VWF	VWF: 311 (278–354)† ADAMTS13: 71 (56–89)† (severe AKI)	Lower ADAMTS13/VWF ratio in patients with severe AKI and those who developed severe COVID-19
Arulkumaran et al.,[55] 2020	7 critically ill patients with COVID-19 and ARDS versus 7 matched controls. VWF elevated, ADAMTS13 normal, and VWF/ADAMTS13 ratio high. After 5 days of PEx, values improved significantly. 5/7 controls developed AKI versus 0/7 PEx treated	VWF: 330 (190–490)† ADAMTS13: 73 (65–89)† VWF/ADAMTS13 = 4.0 (2.8–5.7)	PEx treatment potentially reduced VWF and VWF/ADAMTS13 ratio, with clinical improvement in patients with COVID-19

Table 2 continued.

Study	Main findings	VWF:Ag, ADAMTS13 levels in COVID-19	Link to COVID-19 severity
Delrue et al.,[56] 2020	133 patients with COVID-19. VWF elevated in all patients in both cohorts but higher in VTE cohort. ADAMTS13 levels lowest in VTE cohort. ADAMTS13 also significantly lower in non-survivors versus survivors	VWF: 522 (411–672)† ADAMTS13: 59 (39–701)† (VTE COVID-19 cohort)	VWF higher in VTE cohort and ADAMTS13 lower in VTE cohort than non-VTE cohort. ADAMTS13 also significantly lower in non-survivors versus survivors
Fernández-Pérez et al.,[57] 2021	142 hospitalised patients with COVID-19. VWF/ADAMTS13 ratio seemed to account for severity, given association with clinical scores, hypercoagulable state, ARDS, ICU admission, and mortality. Patients with lower ADAMTS13 activity (<63%) had lower survival	Not reported (values plotted)	"VWF/ADAMTS13 axis imbalance may have an impact on patient's prognosis"
Rodríguez et al.,[58] 2021	100 consecutive hospitalised patients with COVID-19. Severe cases and non-survivors had significantly lower ADAMTS13 activity and higher VWF than non-severe cases and survivors. ADAMTS13 activity negatively correlated with VWF:Ag. 15/19 non-survivors had ADAMTS13 activity <61%	VWF: 395 (294–400)† ADAMTS13: 42 (34–57)† (non-survivors COVID-19)	Significantly lower ADAMTS13 activity and higher VWF in severe cases and non-survivors than non-severe cases and survivors, respectively
De Jongh et al.,[59] 2021	16 patients admitted to ICU with COVID-19. Significantly higher active VWF and significantly lower ADAMTS13 in non-survivors	VWF: 260 (13)‡ ADAMTS13: reported in ng/mL	Significantly higher active VWF and significantly lower ADAMTS13 in non-survivors compared to survivors
De Cristofaro et al.,[60] 2021	10 patients with COVID-19 pneumonia versus 10 patients without COVID-19 pneumonia. VWF significantly elevated in patients with COVID-19 pneumonia. ADAMTS13 normal in both groups. ADAMTS13/VWF significantly lower in patients with COVID-19 pneumonia	VWF: 324 (272–416)† ADAMTS13: 69 (63–74)† (COVID-19 pneumonia)	VWF significantly elevated and ADAMTS13/VWF significantly lower in patients with COVID-19 pneumonia versus patients without COVID-19 pneumonia

*Mean (minimum–maximum).

†Median (interquartile range).

‡Mean (± standard deviation).

Numerical values are given in U/dL (= % of normal).

ADAMTS13: a disintegrin and metalloproteinase with a thrombospondin type 1 motif, member 13; AKI: acute kidney injury; ARDS: acute respiratory distress syndrome; DVT: deep vein thrombosis; ICU: intensive care unit; PE: pulmonary embolism; PEx: plasma exchange; VTE: venous thromboembolism; VWF: von Willebrand factor; VWF:Ag: von Willebrand factor antigen.

Literature Review

A PubMed search of (["VWF" OR "ADAMTS13"] AND "COVID-19"), using various configurations of these search words, identified 77 reports as at 30th January 2021. No language restrictions were imposed but all retrieved reports were in English. The reports were screened by the lead author using the title and abstract or, in the case of no abstract, by review of the full citation. After exclusion of irrelevant papers (i.e., those not reporting on VWF or ADAMTS13 in COVID-19), reviews and commentaries without any original data on VWF or ADAMTS13 in COVID-19, and single-case studies, 17 papers were identified that reported on VWF in COVID-19,[25-41] 3 that

reported on ADAMTS13 and COVID-19,[42-44] and 16 that reported on both VWF and ADAMTS13 in COVID-19.[45-60]

Results of the Literature Review

The results of the literature review are summarised in Table 2. A unifying theme in the reporting papers was elevation of VWF levels and activity in patients with severe COVID-19. That is, all papers identifying VWF levels (antigen or activity) in patients with COVID-19 reported elevated VWF, with levels higher than 600 U/dL in some cohorts, as opposed to normal reference ranges approximating 50–200 U/dL, thus representing a 2–6-fold increase over normal levels. In addition, some reports also identified an association between VWF level and severity of COVID-19, including VWF being higher in non-survivors as opposed to survivors, higher in those admitted to intensive care units as opposed to general wards, and higher in those with greater oxygen requirements (i.e., high-flow oxygen or invasive ventilation). Findings were mixed regarding the linkage of VWF to thrombosis risk per se. For example, Poissy et al.[26] reported that higher VWF:Ag was associated with a greater PE risk, Sweeney et al.[51] reported that patients with thrombosis exhibited significantly higher VWF activity, and Delrue et al.[56] reported higher VWF:Ag in those with venous thromboembolism. In contrast, both Rauch et al.[32] and Ward et al.[37] reported that the association of VWF:Ag to thrombosis was non-significant. These heterogenous findings may be attributable to the type of thrombosis as well as the inflammatory state, which is always a confounder in VWF measurements. Thus, VWF is a well-recognised acute phase reactant and is increased in a variety of inflammatory states.[61] On the other hand, VWF is not the only acute phase protein; factor VIII and fibrinogen both increase acutely following viral infections, including COVID-19, and may thus also fuel prothrombotic outcomes.[62] Additional explanations for these heterogenous findings include the composition, number, and pathophysiological status of the COVID-19 population cohort under investigation, which was broad in terms of included cases. Most of the studies assessing thrombosis were based on venous thromboembolism, as potentially reflected by PE or deep vein thrombosis. These types of thromboses may become evident by standard clinical investigation such as (Doppler) ultrasound, plethysmography, angiography, lung ventilation scan, or CT scan. However, it is the formation of microthrombosis that elevated VWF may be preferentially causing, as may be anticipated in thrombotic microangiopathies. Microthrombi are more difficult to assess clinically and instead may only be evident in autopsy reports.[12,14,15,24]

Where ADAMTS13 was evaluated in patients with COVID-19, this was either found to be at normal levels or reduced. In some cases, levels were low enough to be consistent with a secondary thrombotic microangiopathy, including a TTP-like syndrome, with ADAMTS13 levels occasionally reaching <10%. Where antibodies to ADAMTS13 were evaluated, these were generally not found. Thus, the picture essentially reflects an ADAMTS13 consumption event, likely associated to the level of VWF and presence of endothelial activation rather than an autoimmune picture like in acquired TTP.[4]

Overall, VWF elevation has been more consistently observed in the literature than has a reduction in ADAMTS13 (Table 2). However, looking at VWF or ADAMTS13 alone, without consideration of the other, could lead to misrepresentative findings and explain some of the differences observed between studies. Indeed, a significant increase in VWF level alone (without any evident reduction in ADAMTS13 level) would still lead to an imbalance of the VWF/ADAMTS13 axis and ultimately infer a prothrombotic risk (Figure 1D). Although ADAMTS13 may be in the normal range (approximating 50–150 U/dL), it is likely that a reduction may still be occurring in many of these patients relative to their own baseline (pre-COVID-19) levels of ADAMTS13.

Many investigations formally looking at the VWF/ADAMTS13 axis in COVID-19 have reported an association with worse outcomes. For example, Bazzan et al.[47] found that patients with COVID-19 who died had significantly lower levels of ADAMTS13 and higher levels of VWF compared to those with non-fatal outcomes. Sweeney et al.[51] also reported that non-survivors had significantly lower ADAMTS13 activity levels and higher VWF, with ADAMTS13 activity inversely correlated with VWF. Additionally, the number of patients requiring ventilation with initial ADAMTS13 <43% was more than twice that of those with initial

ADAMTS13 above this threshold.[51] Mancini et al.[53] also reported that the VWF/ADAMTS13 ratio was associated with COVID-19 disease severity (medians of 3.42, 6.77, and 8.33 in low, medium, and high severity, respectively). Rodríguez et al.[58] reported significantly lower ADAMTS13 activity and higher VWF (thus, elevated VWF/ADAMTS13) in severe cases and non-survivors as compared to non-severe cases and survivors, respectively. De Jongh et al.[59] similarly reported significantly higher active VWF and significantly lower ADAMTS13 in non-survivors versus survivors. Furthermore, De Cristofaro et al.[60] reported that VWF was significantly elevated and ADAMTS13/VWF significantly lower (i.e., VWF/ADAMTS13 higher) in patients with COVID-19 pneumonia versus patients without COVID-19 pneumonia. Finally, Henry et al. reported a lower ADAMTS13/VWF ratio (equivalent to a higher VWF/ADAMTS13 ratio) in those who developed severe COVID-19 and in those who developed severe AKI, a hallmark of thrombotic microangiopathies. [54]

Further research is still needed to fully understand the mechanisms associated with the prothrombotic state in COVID-19. This includes studying how the VWF/ADAMTS13 axis imbalance is connected to the intermingled mechanisms of SARS-CoV-2 pathophysiology, such as immune dysregulation, complement overactivation, neutrophil extracellular traps, and auto-antibodies, which may all converge to propagate COVID-19-associated coagulopathy.[12]

There were several striking disparities in terms of data reporting that complicated assessment of the commutability between studies. Firstly, although VWF was usually reported as the level of antigen and ADAMTS13 as the level of activity, sometimes authors instead reported VWF activity and ADAMTS13 antigen. Secondly, although VWF:Ag and ADAMTS13 activity were most often reported, these tests were performed using a wide range of methodologies. For instance, VWF:Ag was assessed using both commercial and in-house enzyme-linked immunosorbent assays, commercial latex immunoassays, and chemiluminescence immunoassays. These utilise different capture and detection antibodies and different assay calibrators, thus affecting both normal reference range data as well as arising values in patients with COVID-19. When reported, VWF activity was even more varied and included ristocetin cofactor assays or other platelet glycoprotein Ib (GPIb) binding assays, such as VWF:GPIbR (recombinant) or VWF:GPIbM (mutant). Collagen binding activity was rarely reported. ADAMTS13 activity was measured using in-house or commercial fluorescence resonance energy transfer methods and chemiluminescence immunoassays. Sometimes, methods used were not described at all, which made comparisons between studies essentially impossible.

Despite discussing the imbalance between VWF and ADAMTS13 in COVID-19, very few reports provided values for either VWF/ADAMTS13 or ADAMTS13/VWF ratios, which the authors believe will become an important parameter in a variety of pathophysiological states, including COVID-19. The authors thus call on future researchers to report such values more widely in the future.

Lastly, the authors considered the wide variety of grades of COVID-19 severity. This condition develops throughout a vast array of clinical pictures, ranging from totally asymptomatic or paucisymptomatic (e.g., only causing influenza-like symptoms), then progressing to lower respiratory tract involvement (interstitial pneumonia), and finally evolving into a systemic disorder that may ultimately lead to multi-organ failure and death.[63] Since thrombosis is a hallmark of the evolving pathology, it is likely that the degree of impairment of the VWF/ADAMTS13 axis would progress in parallel with disease worsening.

Further Therapeutic Developments

A secondary thrombotic microangiopathy requires treatment of the driving force (presumably COVID-19 in this instance). The above observations therefore pave the way to evaluating specific therapies already used in secondary microangiopathies, such as complement inhibitors (e.g., eculizumab). Although other similar agents, including ravulizumab, have not been overly successful in trials for COVID-19, preliminary data suggest that this therapeutic approach may complement others to improve survival and lower hypoxia, especially in patients with COVID-19 and severe illness or ARDS,[64-66] thus suggesting that secondary thrombotic microangiopathy may be a major driver of outcomes in SARS-CoV-2

infection. The use of recombinant ADAMTS13 is another possible option to lower abnormally upregulated VWF factor in the plasma of patients with COVID-19, as recently highlighted by Turecek et al.;[67] however, this would need to be tested in future trials. Also of relevance is the small study by Arulkumaran et al.,[51] who utilised plasma exchange in seven critically ill patients with COVID-19 and ARDS versus seven matched controls, and who not only showed improvement in patients after plasma exchange but also noted that the majority (n=5/7) of controls developed AKI, whereas AKI was developed by none of the seven plasma-exchange-treated patients. Thus, therapies normally used in TTP may also be useful in the management of COVID-19.

CONCLUSION

In summary, recent evidence strongly suggests that COVID-19 can progress towards a thrombotic disorder, characterised by both micro- and macrothrombosis in the lungs, as well as in many other organs and tissues.[12-15] The development of any form of thrombosis, which can then have a strong impact on a patient's prognosis, appears to be accompanied by an imbalance of VWF and ADAMTS13, evidenced by a high VWF/ADAMTS13 ratio, thus generating a clinical picture that closely resembles a secondary thrombotic microangiopathy. The authors highly recommend reporting of VWF/ADAMTS13 ratios in future COVID-19 studies to give additional context to the altered VWF/ADAMTS13 axis in these patients.

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Management of Multiple Myeloma in Older Patients

Authors: *Jian Li, Henry Chan

Waitemata District Health Board, Auckland, New Zealand
*Correspondence to jli196@yahoo.co.nz

Disclosure: The authors have declared no conflicts of interest.

Received: 06.10.20

Accepted: 26.01.21

Keywords: Frailty, geriatric, gerontology, haematology, myeloma, older.

Citation: EMJ Hematol. 2021;9[1]:69-81.

Abstract

Multiple myeloma is a condition that affects predominantly the older population. There are now various approved chemotherapy regimens as a result of advances in treatment. Choosing the optimal regimen for older patients with myeloma remains a challenge because of frailty and a lack of head-to-head comparisons between backbone regimens. The purpose of this literature review is to summarise the recent literature on frailty assessment, disease biology, and treatment efficacy in the frontline and relapsed settings to aid the decision-making process.

INTRODUCTION

Multiple myeloma is a haematological malignancy predominantly affecting older people and has a median age of onset of 70 years.[1] Traditionally, the term 'elderly' in myeloma applied to those aged over 65–70 years, as these patients were considered as transplant-ineligible. However, this is a heterogeneous group of patients with varying degrees of fitness, physiological reserve to tolerate treatment, and life expectancy. In recent years, there have been renewed interests in this group of patients, with specifically designed prospective trials to determine treatment outcomes and tolerability, and research on the impact of frailty amongst these patients. This review aims to summarise key findings from the literature on older patients with myeloma, including frailty assessment, disease biology, and chemotherapy treatment in the frontline and relapsed settings.

METHODS

A literature search using the keywords "elderly", "frailty", "myeloma", and "transplant-ineligible" was conducted in Google Scholar, PubMed, and Medline. Articles written in English were included and a preferential focus was placed on Phase III clinical trials and systematic reviews that were published within the last 10 years. Preliminary analyses, Phase I/II trials, post hoc analyses, and commentaries were included if they contained relevant merits.

FRAILTY ASSESSMENT

Frailty is a cumulative state of physiological decline associated with ageing. It has been reported that frail individuals have a reduced physiological reserve to external insult such as chemotherapy.[1,2] One of the earlier definitions of frailty was described by Fried et al.[3] as having three of the following five components: unintentional weight loss, poor grip strength,

self-reported exhaustion, slow mobility, and a low level of physical activity. Since then, several surrogate scoring tools have been developed for predicting frailty amongst patients with myeloma (Table 1).

The International Myeloma Working Group (IMWG) frailty assessment tool was developed based on a cohort of 869 transplant-ineligible (TI) patients with myeloma (Table 1).[4] The frail score was composed of age categories, Katz Activity of Daily Living (ADL), Instrumental Activity of Daily Living (IADL), and Charlson Comorbidity Index (CCI). Three groups were identified: fit (score of 0), intermediate fit (score of 1), and frail (score of ≥2). This tool was predictive of 3-year overall survival (OS) (84% in fit; 76% in intermediate fit; and 57% in frail patients), serious treatment-related events, and incidence of treatment discontinuation.[4] The Revised Myeloma Comorbidity Index (R-MCI) is an updated version of the Initial Myeloma Comorbidity Index, with additional information on adverse cytogenetics and frailty assessment (Table 1).[5] The score was internally validated to predict median OS (10.1 years in the fit group; 4.4 years in the intermediate fit group; and 1.2 years in the frail group).[5]

Table 1: Frailty assessment tools in multiple myeloma.

Items measured	Frailty groups	Prognostication in myeloma in derivation cohort
IMWG tool[4]		
1. Age in years: ≤75 scores 0; 76–80 scores 1; >80 scores 2 2. ADL: >4 scores 0; ≤4 scores 1 3. IADL: >5 scores 0; ≤5 scores 1 4. CCI: ≤1 scores 0; ≥2 scores 1	Fit (score of 0) Intermediate fit (score of 1) Frail (score ≥2)	3-year OS: 84% in fit; 76% in intermediate fit (HR=1.61; p=0.042); 57% in frail (HR: 3.57; p<0.001) 3-year PFS: 48% in fit; 41% in intermediate fit (HR: 1.18; p=0.211); 33% in frail (HR: 1.68; p<0.001) Grade ≥3 non-haematological AE (intermediate fit HR: 1.13, p=0.462; frail HR: 1.57, p=0.008)
R-MCI[5]		
Renal function ($eGFR_{MDRD}$): <60 scores 1 Moderate/severe lung disease (dyspnoea or lung function): scores 1 KPS: 80–90% scores 2; ≤70% scores 3 Age in years: <60 scores 0; 60–69 scores 1; ≥70 scores 2 Frailty defined by Fried: ≥2 factors scores 1 Unfavourable cytogenetics: scores 1	1. Fit (score ≤3) 2. Intermediate fit (score of 4–6) 3. Frail (score	Median OS: 10.1 years in fit; 4.4 years in intermediate fit; 1.2 years in frail Median PFS: 4.1 years in fit; 1.9 years in intermediate fit; 0.9 years in frail
GAH scale[6]		
Polypharmacy: ≥5 medications scores 1Gait speed over 4 metres: <0.8 m/sec scores 1 Depressed mood: item from CES-D scores 1 ADL: requires help in at least one area scores 1 Subjective health status: poor or fair scores 1 Nutrition: items score of ≤8 scores 1 in the scale Mental status (SPMSQ): ≥3 errors scores 1 Comorbidities index: ≥3 scores 1	Score ≤1 Score 2–6 Score >6	Predictive of survival of patients with haematological malignancies (n=164) in a cohort of 363 patients. Amongst them, 60 patients had myeloma.

Items measured	Frailty groups	Prognostication in myeloma in derivation cohort
MHOS Frailty Index[7]		
Activities of daily living (4 items) Chronic health conditions (9 items) Functioning (7 items) General health (3 items) Mental health (2 items)	Score ranges from 0 (no frail deficits) to 1 Considered as frail if index score is above the predicted mean for age	Median OS: 26.8 months in frail patients with myeloma; 43.7 months in non-frail patients; p=0.015 Each 10% increase in Frailty Index score was associated with a 16% increased risk of death (aHR: 1.16; p<0.001)
UK-MRP[8]		
WHO performance status (scores from -0.398 to 0.397) ISS (scores from -0.212 to 0.212) Age CRP	1. Fit (scores < -0.256) 2. Intermediate fit (scores -0.256 to -0.0283) 3. Frail (scores >-0.0283	Median OS in NCRI-XI: 60 months in fit; 44 months in intermediate frail; 25 months in frail Median OS in MRC-IX: 49 months in fit; 34 months in intermediate fit; 20 months in frail Median PFS in NCRI-XI: 20 months in fit; 17 months in intermediate fit; 12 months in frail Median PFS in MRC-IX: 15 months in fit; 13 months in intermediate fit; 9 months in frail

ADL: Katz activity of daily living; AE: adverse event; aHR: adjusted HR; CCI: Charlson Comorbidity Index; CES-D: Center For Epidemiologic Studies Depression Scale; CRP: C-reactive protein; $eGFR_{MDRD}$: estimated glomerular filtration rate calculated using the modification of diet in renal disease study equation; GAH: Geriatric Assessment in Hematology; HR: hazard ratio; ISS: international staging system; MHOS: Medicare Health Outcomes Survey; MRC-IX: Medical Research Council Myeloma IX trial; NCRI-XI: National Cancer Research Institute Myeloma XI study; IADL: instrumental activity of daily living; IMWG: International Myeloma Working Group; KPS: Karnofsky performance status; OS: overall survival; PFS: progression-free survival; R-MCI: Revised Myeloma Comorbidity Index; SPMSQ: Short Portable Mental Status Questionnaire; UK-MRP: UK Myeloma Research Alliance Risk Profile; WHO: World Health Organization.

It remained predictive of survival outcomes in the younger subgroup (age <65 years).[5] This emphasised that frailty was not limited to older patients.

These tools are not without shortfalls. The ADL and IADL assessments of the IMWG tool can take on average 15–20 minutes to complete, which affects its adoption in day-to-day clinical practice.[9] Meanwhile, the score appeared to have limited ability to predict OS when applied to a separate cohort of patients aged ≥75 years.[10] There was also inconsistency across different frailty tools, with the IMWG tool classifying more patients into the frail category than R-MCI and CCI.[11]

Simplified tools have been proposed to address the time constraint issue in frailty assessment at a day-to-day clinical practice. The first group, including the Geriatric Assessment in Haematology (GAH) Scale and the Medicare Health Outcomes Survey (MHOS) Frailty Index, were based on self-reported elements (Table 1). The former was a 30-item list shown to predict mortality in haematology patients.[6] The latter derived 25 questionnaire items on ADL, chronic health conditions, functional status, subjective general health, and mental health. Every 10% increase in the frailty index predicted a 16% increased risk of death in patients with newly diagnosed myeloma aged >65 years.[7] Although these surveys can be completed before clinic attendance, they rely heavily on patients' subjective assessment, which can be a source of bias.

Another approach is to use performance-based assessment such as gait speed, which can be easily obtained using the 4 m gait speed test

developed by the National Institutes of Health (NIH).[12] In a recent analysis of patients aged ≥75 years with a haematological malignancy, reduced gait speed was associated with increased mortality, hospitalisation, and emergency visits.[13] In a study of prognostication in patients with myeloma, performance status (PS) consistently contributed to survival outcomes regardless of their age groups.[14] A simplified frailty score based on a patient's age, CCI, and Eastern Cooperative Oncology Group (ECOG) PS was retrospectively analysed from the FIRST trial cohort and showed frail patients experienced worse PFS, OS, and more treatment-related adverse events.[15] The performance of this score was validated in an independent dataset from the HOVON87/NMSG18 study with 636 TI patients.[16] Similarly, in a post hoc analysis of the ASPIRE and ENDEAVOR trials, frailty score based on age, CCI, and PS appeared to show worse PFS and OS in frail inviduals.[17] Some studies explored the use of biomarkers in frailty assessment. For example, the UK Myeloma Research Alliance Risk Profile (UK-MRP) was based on the non-intensive arms of NCRI-Myeloma-XI and MRI-IX trials and found that World Health Organization (WHO) PS, International Staging System (ISS), age, and C-reactive protein were associated with progression-free survival (PFS), early mortality, and the percentage of treatment dose delivered (Table 1).[8] Although these models appeared to show prognostic significance, some weighed more heavily towards disease characteristics. PS-based assessments are convenient for use in a day-to-day clinical setting; however, they may not encompass the full spectrum of the frailty phenotype and can be subjective.[18]

Despite a lack of consensus on an ideal frailty assessment tool in a day-to-day clinical practice, the above data indicated that some form of frailty assessment would provide prognostic information on older patients with myeloma. Questions remain on tailoring treatment based on frailty; hopefully, data from the FRAIL-M study and the UK MRC-XIV study[19] will provide further insight.

FRONTLINE THERAPY

Novel agents such as bortezomib and lenalidomide had been established as the standard of care. The addition of bortezomib to melphalan and prednisolone (VMP) for TI patients in the VISTA study showed survival benefit even in those aged ≥75 years (Table 2).[20] A reduced once-weekly bortezomib dosing showed a reduction of neuropathic and gastrointestinal adverse effects without affecting efficacy.[31] Meanwhile, continuous lenalidomide and dexamethasone (Rd) became an established regimen after demonstrating superior PFS and OS over the previous standard of care of a melphalan, prednisolone, and thalidomide regimen in the FIRST trial (Table 2).[22,32] Addition of an alkylating agent to the Rd regimen did not show superiority in the EMN01 study unless the patient was classified as fit according to the IMWG tool.[23,33]

Regimens combining immunomodulatory drugs (IMiD) and bortezomib were investigated for their synergistic effect. Bortezomib and thalidomide combination (VTP) demonstrated a higher incidence of Grade ≥3 cardiac complications (8% versus 0% in the VMP group), offsetting the potential benefit.[34] In the UPFRONT study, bortezomib, thalidomide, and dexamethasone (VTD) did not show superior OS to the VMP regimen but more neuropathy, whilst the doublet combination of bortezomib and dexamethasone had comparable efficacy (Table 2).[24] Using lenalidomide with bortezomib appeared to be more favourable, with better tolerance than thalidomide. The combination of lenalidomide, bortezomib, and dexamethasone demonstrated superior survival outcome and duration of response than Rd alone in the SWOG-S0777 trial (Table 2).[25] However, the study population was generally younger (median age of 63 years) than what was considered as 'elderly', and 10% proceeded for autologous transplant. Subgroup analysis from the SWOG-S0777 trial demonstrated significant overall survival benefit but not PFS benefit in those aged >75 years, whilst neurological toxicity was significantly more prevalent with bortezomib (33% versus 11% in Rd).[25]

Table 2: Upfront chemotherapy treatment, dosage regimens, and efficacy in older patients with myeloma.

Trial (year)	Treatment dose regimens	Efficacy
VISTA (2008)[20]	6-weekly cycle, total of 9 cycles Bortezomib: 1.3 mg/m^2 IV Day 1, 4, 8, 11, 22, 25, 29, 32 (Cycle 1–4); Day 1, 8, 22, 29 (Cycle 5–9) Melphalan: 9 mg/m^2 Day 1–4 Prednisolone: 60 mg/m^2 Day 1–4	Median OS: 56.4 months versus 43.1 months in MP Median time to next treatment: 27 months versus 19.2 months in MP Median treatment-free interval: 16.6 months versus 8.3 months in MP
RVd-Lite (2014)[21]	35-day cycle Bortezomib: 1.3 mg/m^2 weekly subcutaneous Day 1, 8, 15, 22 Lenalidomide: 15 mg Day 1–21 Dexamethasone: 20 mg Day 1, 2, 8, 9, 15, 16, 22, 23 for <75 years of age; Day 1, 8, 15, 22 for age ≥75 years	Median PFS: 35.1 months Median OS: not reached after 30 months ORR: 91.4%
FIRST (2014)[22]	28-day cycles, continuous or 18 cycles Lenalidomide: 25 mg Day 1–21 Dexamethasone: 40 mg Day 1, 8, 15, 22 42-day cycle, total of 12 cycles Melphalan: 0.25 mg/kg Day 1–4 Prednisolone: 2 mg/kg Day 1–4 Thalidomide: 200 mg daily	Median PFS: 26 months in Rd continuous; 21 months with Rd18; and 21.9 months with MPT Median OS: 59.1 months for Rd continuous; 62.3 months for Rd18; 49.1 months for MPT ORR: 81% in Rd continuous; 79% in Rd18; 67% in MPT
EMN01 (2014)[23]	28-day cycle, total of 9 cycles of induction MPR Lenalidomide: 10 mg Day 1–21 Melphalan: 0.18 mg/kg Day 1–4 for 65–75 years of age; 0.13 mg/kg for those >75 years Prednisolone: 1.5 mg/kg Day 1–4 CPR Lenalidomide: 10 mg Day 1–21 Cyclophosphamide: 50 mg alternating days for 28 days in ages 65–75 years; 21 days in ages >75 years Prednisolone: 25 mg alternating days Rd Lenalidomide: 25 mg Day 1–21 Dexamethasone: 40 mg Day 1, 8, 15, 22 in ages 65–75 years; 20 mg in those aged >75 years Maintenance either lenalidomide 10 mg Day 1–21 or in combination with prednisolone 25 mg every other day	Median PFS: 24 months in MPR; 20 months in CPR; 21 months in Rd 4-year OS: 65% in MPR; 68% with CPR; 58% with Rd ORR: 71% in MPR; 68% in CPR; 74% with Rd

Trial (year)	Treatment dose regimens	Efficacy
UPFRONT (2015)[24]	21-day cycle, total of 8 cycles VD Bortezomib: 1.5 mg/m^2 IV Day 1, 4, 8, 11 Dexamethasone: 20 mg Day 1, 2, 4, 5, 8, 9, 11, 12 (Cycle 1–4); Day 1, 2, 4,5 (cycle 5–8) VTD Thalidomide: 100 mg Day 1–21 VMP Melphalan: 9 mg/m^2 Day 1–4 Prednisolone: 60 mg/m^2 Day 1–4 Maintenance with bortezomib IV 1.5 mg/m^2 Day 1, 8, 15, 22	Median PFS: 14.7 months in VD; 15.4 months in VTD; 17.3 months in VMP (p=0.46) ORR over 13 cycles: 73% in VD; 80% in VTD; 70% in VMP Median OS: 49.8 months in VD; 51.5 months in VTD; 53.1 months in VMP (p=0.79)
SWOG-S07777 (2017)[25]	21-day cycle, total of 8 cycles Bortezomib: 1.3 mg/m^2 IV Day 1, 4, 8, 11 Lenalidomide: 25 mg Day 1–14 plus 20 mg Day 1, 2, 4, 5, 8, 9, 11, 12 Dexamethasone: 40 mg Day 1, 8, 15, 22 28-day cycle, total of 6 cycles Lenalidomide: 25 mg Day 1–21 Dexamethasone: 40 mg Day 1, 8, 15, 22	Median PFS: 43 months versus 30 months in Rd (HR: 0.712; p=0.0037) Median response duration: 52 months versus 38 months in Rd (HR=0.695; p=0.0133) Median OS: 75 months versus 64 months in Rd (HR: 0.709; p=0.0125)
TOURMALINE-MM2 (2020)[26]	28-day cycle, total of 18 cycles Ixazomib: 4 mg or placebo on Day 1, 8, 15 Lenalidomide: 25 mg Day 1–21 (10 mg for those with renal impairment) Dexamethasone: 40 mg Day 1, 8, 15 and 22 (20 mg if aged >75 years) After 18 cycles, dexamethasone was discontinued and treatment continued with ixazomib 3 mg and lenalidomide 10 mg	Median PFS: 35.3 months in IRd versus 21.8 months in Rd (HR: 0.83; p=0.073) ORR: 82.1% in IRd versus 79.7% in Rd (HR: 1.16; p=0.436). CR/sCR: 25.6% in IRd versus 14.1% in Rd (HR: 2.10; p<0.001)
CLARION (2019)[27]	42-day cycle, total of 9 cycles Carfilzomib: IV Day 1, 2, 8, 9, 22, 23, 29, 30 at 20 mg/m2 on Day 1, 2 of Cycle 1 and 36 mg/m^2 thereafter; OR bortezomib 1.3 mg/m^2 subcutaneous or IV on Day 1, 4, 8, 11, 22, 25, 29, 32 for cycle 1–4; Day 1, 8, 22, 29 for Cycle 5–9 AND Melphalan: 9 mg/m^2 Day 1–4 Prednisolone: 60 mg/m^2 Day 1–4	Median PFS: 22.3 months versus 22.1 months in VMP (p=0.1590) ORR: 84.3% versus 78.8% in VMP (p=0.02)
AGMT-MM-02 (2020)[28]	Carfilzomib: 20 mg/m^2 on Day 1, 2; 27 mg/m^2 on Day 8, 9, 15, 16 for Cycle 1; 27 mg/m^2 on Day 1, 2, 8, 9, 15, 16 for Cycle 2; 56 mg/m^2 on Day 1, 8, 15 for Cycle 3–9 Dexamethasone: weekly (20 mg in patients aged ≥75 years) Lenalidomide: 25 mg Day 1–21 OR thalidomide 100 mg Day 1–28 (50 mg in patients aged ≥75 years) After 9 cycles of chemotherapy, randomised to either carfilzomib 56 mg/m^2 on Day 1 and Day 15 every 4 weeks or observation for 1 year	Interim analysis ORR: 96.6% PFS: 22.3 months 24-month OS: 78.0%

Trial (year)	Treatment dose regimens	Efficacy
ALCYONE (2018)[29]	42-day cycle, total of 9 cycles Daratumumab: 16 mg/kg IV weekly in Cycle 1; every 3 weeks in Cycle 29; and every 4 weeks until stop Bortezomib: 1.3 mg/m^2 subcutaneously twice weekly on Week 1, 2, 4, 5 of Cycle 1 and once weekly on Week 1, 2, 4, 5 of Cycle 2–9 Melphalan: 9 mg/m^2 Day 1–4 Prednisolone: 60 mg/m^2 Day 1–4	36-month OS: 78% versus 67.9% in VMP HR for death: 0.60 (p=0.0003) HR for PFS: 0.42 (p=0.0001) ORR: 90.9% versus 73.9% in VMP (p<0.0001)
MAIA (2019)[30]	28-day cycle Daratumumab: 16 mg/kg IV weekly Cycle 1–2; every 2 weeks in Cycle 3–6; every 4 weeks after Lenalidomide: 25 mg Day 1–21 (10 mg in those with reduced creatine clearance) Dexamethasone: 40 mg weekly	Median PFS not reached versus 31.9 months in Rd HR for disease progression or death: 0.56 (p<0.001). ORR: 92.9% versus 81.3% in Rd (p<0.001)

CPR: cyclophosphamide, prednisolone, and thalidomide; CR/sCR: complete response/stringent complete response; HR: hazard ratio; IRd: ixazomib, lenalidomide, and dexamethasone; IV: intravenous; MP: melphalan and prednisolone; MPR: melphalan, prednisolone, and lenalidomide; MPT: melphalan, prednisolone, and thalidomide; ORR: objective response rate; OS: overall survival; PFS: progression-free survival; Rd: lenalidomide and dexamethasone; Rd18: lenalidomide and dexamethasone for 18 cycles; VD: bortezomib and dexamethasone; VMP: bortezomib, melphalan, and prednisolone; VTD: bortezomib, thalidomide, and dexamethasone.

In another study, O'Donnell et al.[21] demonstrated this regimen can be dose-reduced in older patients (bortezomib: 1.3 mg/m^2 subcutaneous weekly; lenalidomide: 15 mg on Day 1–21; and dexamethasone: 20 mg) and achieved comparable PFS of 35 months (Table 2).[21] Only one patient from a cohort of 50 experienced Grade 3 peripheral neuropathy.[21] These data support a bortezomib and lenalidomide combination as an efficacious upfront treatment option for fit, older patients with myeloma, which can be dose-adjusted to increase tolerability.

Carfilzomib was combined with melphalan and prednisolone in the CLARION study for the TI group against VMP. There were no significant differences between the two regimens in the median PFS, time to progression, response rate, median duration of response, and measurable residual disease (MRD) (Table 2). More patients in the regimen containing carfilzomib discontinued treatment because of adverse effects (16.7% versus 14.7%), while the VMP regimen had a high incidence of neuropathy (35.1% versus 2.5%; p<0.0001). The authors suggested once-weekly carfilzomib rather than twice weekly might increase its tolerability.[27] A recent interim analysis from the AGMT-MM-02 study showed that older TI patients with myeloma who received twice weekly carfilzomib for two cycles followed by weekly carfilzomib at 56 mg/m^2 from Cycle 3 to 9 in combination with IMiDs and dexamethasone experienced high objective response rate (ORR; 96.6%), whilst, 47.1% of participants had achieved deep response as measured by negative MRD (Table 2).[28]

Daratumumab, an anti-CD38 antibody, is emerging as a frontline treatment candidate. The addition of daratumumab to VMP showed higher response rates, higher incidence of negative MRD, prolonged PFS, and better OS in the ALCYONE study (Table 2).[29,35] Meanwhile, the MAIA study investigated the addition of daratumumab to Rd in TI patients. It showed a superior event-free survival, ORR, and negative MRD status (Table 2).[30] Both trials demonstrated higher infection rates in the daratumumab groups, especially respiratory infections.[29,30,35] In a recent meta-analysis of upfront regimens for older TI patients with myeloma, daratumumab combinations appeared to be the most efficacious in prolonging PFS.[36]

The aforementioned frailty assessment may help determine the optimal frontline chemotherapy regimen for older patients with myeloma. Fit patients appeared to benefit from lenalidomide triplet as opposed to Rd alone based on data from a post hoc analysis of the EMN01 trial.[33]

Although there was no head-to-head comparative trials, a pooled analysis by Larocca et al.[37] compared bortezomib-based regimens against Rd (with maintenance lenalidomide). It showed no difference in survival outcomes for patients with standard-risk cytogenetics but improved outcomes for those with high-risk cytogenetics receiving VMP. Interestingly, those aged >75 years with standard cytogenetics appeared to gain benefit from the Rd-based regimen as opposed to the younger counterparts who benefited more from VMP.[37]

Consideration of treatment toxicity profile can influence the choice of regimens. Continuous Rd in the FIRST trial showed a lower rate of neutropenia (30% versus 45% in melphalan, prednisolone, and thalidomide); however, a longer period of chemotherapy exposure might contribute to a higher rate of Grade 3 or 4 infections (32% versus 17% in melphalan, prednisolone, and thalidomide).[32] Cardiac toxicity from the VTP regimen would limit its tolerability in older patients as they are more likely to have pre-existing cardiac comorbidities.[34] Peripheral neuropathy and gastrointestinal toxicity from bortezomib can be less tolerated in older and frail patients. These issues continue to encourage studies of new chemotherapy regimens for older patients with myeloma.

Ixazomib is an oral proteasome inhibitor with the advantages of less hospital attendance for infusion and the potential for use as a maintenance treatment. The results from the Phase III TOURMALINE-MM02 study in TI patients with myeloma showed a median PFS of 35.3 months in the ixazomib, lenalidomide, and dexamethasone arm compared with 21.8 months in the Rd arm (hazard ratio: 0.83; p=0.073); however, the results failed to reach statistical significance (Table 2).[26] In a Phase II HOVON 143 study, a combination of ixazomib, daratumumab, and dexamethasone were studied in unfit and frail patients with myeloma who were classified according to the IMWG criteria. Interim efficacy analysis showed ORR of 87% and 78% in the unfit and frail groups, respectively.[38] Elotuzumab, a monoclonal antibody against SLAMF7, in addition to Rd was recently studied in the ELOQUENT-1 trial. It did not show a significant difference in PFS against Rd.[39] The use of belantamab mafodotin, an antibody–drug conjugate, was studied in the relapsed and refractory settings.[40] The DREAMM-9 study is designed to specifically study its efficacy and safety in combination with bortezomib, lenalidomide, and dexamethasone in TI participants.[41]

QUALITY OF LIFE

Despite the increasing use of novel agents and monoclonal antibodies in older patients with myeloma, it remains an incurable disease with poor survival outcomes. Measurement of the quality of life must be considered in this group. In the FIRST trial, continuous Rd improved health-related quality of life during the first 18 months, which might be maintained beyond this timeframe if treatment continued.[42] In the HOVON-87/NMSG18 study, health-related quality of life was assessed using the EORTC QLQ-C30 and MY20 questionnaires at baseline, induction, and maintenance therapies.[43] Improvement in the quality of life was evident in the lenalidomide-based treatment group during the maintenance phase as opposed to a higher incidence of neuropathy with thalidomide maintenance, which offset its potential benefit in reducing disease progression. In the CLARION study, quality of life measures appeared to favour carfilzomib, especially in the domains of physical function, fatigue, pain, and treatment side effects.[27] In the RVD-lite cohort, patients receiving a reduced-intensity triplet regimen experienced significant improvements in physical function, future perspective, and disease symptoms.[21] Complications from skeletal and extramedullary diseases would impact on the quality of life in myeloma patients; therefore, radiation treatment, anti-resorptive therapies, and early access to palliative care would likely influence patient outcomes.

CYTOGENETICS IN TRANSPLANT-INELIGIBLE PATIENTS

It is recognised that older patients with myeloma have a different tumour genetic profile. The proportion of patients with t(4;14) and del(17p) appeared to lessen in the older age group, while the opposite was observed for those with gain(1q). Molecular study data showed that mutational signatures associated with hyperdiploidy were common with ageing.[44] The impact of t(4;14) and gain(1q) were less in the very old group (>80 years), while del(17p) persistently predicted adverse outcomes across different age groups.[14] The overall impact became smaller with advancing age.[14] Poor PS and frailty predominated over adverse cytogenetic markers in prognosticating those >80 years.[14] This illustrates that genetic markers are not uniform in their prognostic impact with advancing age.

Questions remain as to how best to tailor frontline treatment in TI patients based on the cytogenetic results in the absence of well-designed, risk-adapted studies. A recent post hoc analysis by Larocca et al.[45] compared outcomes between bortezomib- and lenalidomide-based treatment arms from the GIMEMA-MM-03-05 and EMN01 trials based on the cytogenetic results. It showed that bortezomib could overcome cytogenetic adversity of t(4;14) and t(14;16) in TI patients to gain PFS benefit.[45] This was not apparent in those with del(17p).

AUTOLOGOUS TRANSPLANT

Data on the role of autologous stem cell transplant in older patients with myeloma are not as robust because of the use of age threshold and PS as surrogate markers for transplant eligibility. The IFM-99-06 was a prospective study on autologous transplant in older patients.[46] There was no significant survival benefit when comparing reduced-intensity conditioning autologous transplant with a melphalan plus prednisolone regimen. On the other hand, older patients with myeloma showed comparable benefits from autologous transplant to the younger patients.[47]

Non-relapse mortality (NRM) was thought to be higher in patients over the age of 70 years with a conventional melphalan dose of 200 mg/m^2. Trials using a reduced-intensity regimen showed improved outcomes in older patients with myeloma without reducing their efficacy.[48,49] This has been challenged by an analysis of the CIBMTR database, which included 15,999 patients with myeloma during 2013–2017.[50] Age ≥70 years was not demonstrated to have significantly worse NRM (hazard ratio: 1.3; 99% confidence interval: 1.0–1.7). Furthermore, older patients who received reduced dose conditioning had worse outcomes than those receiving a full dose in aspects of Day-100 NRM, 2-year PFS, and 2-year OS.[50]

A more comprehensive approach in selecting transplant candidates is needed than using biological age alone. A Haematopoietic Cell Transplantation Comorbidity Index (HCT-CI) ≥3 was not associated with a worse survival outcome.[51] Using the IMWG classification tool, frailty was associated with cumulative gastrointestinal toxicity and infections.[52]

Overall, efficacy data appeared to support autologous transplant in fit and older patients with myeloma. With the emergence of efficacious and novel chemotherapy regimens, it is unclear whether this efficacy remains relevant in older patients with myeloma.

RELAPSED OR REFRACTORY TREATMENT

Outcomes in older patients with either relapsed or refractory myeloma remain poor, and there were few studies dedicated to this group. Data guiding current management in the relapsed or refractory settings were mostly based on subgroup analyses of clinical trials.

Newer IMiD such as pomalidomide showed efficacy in the relapsed or refractory settings.[53] In the MMWP-164 study, Lee et al.[54] investigated the efficacy of pomalidomide with cyclophosphamide and dexamethasone in older patients with myeloma. The outcome appeared decimal as only 10% of patients remained on treatment at the last follow-up, mostly because of disease progression.[54] The median PFS was 6.9 months and an OS of 18.49 months was recorded.[54] Guarded outcomes were

also observed in younger patients receiving pomalidomide after they experienced relapsed or refractory disease.[55]

The ENDEAVOR trial showed that carfilzomib and dexamethasone were efficacious in the relapsed or refractory settings.[56] In the subgroup analysis of the 17% of patients aged ≥75 years, median PFS was 18.7 months in the carfilzomib group as opposed to 8.9 months in the bortezomib group.[57] Median PFS in the younger subgroup receiving carfilzomib was 15.6 months, suggesting older patients might benefit more from carfilzomib.[57] Carfilzomib was combined with lenalidomide and dexamethasone in the ASPIRE trial; however, no statistically significant difference in PFS was noted in the ≥65 age group when compared with Rd alone.[58] This might be because of a higher discontinuation rate from cardiac toxicity in the carfilzomib group.

Despite recent studies focused on the use of ixazomib in the upfront setting, it was commonly used in the relapsed or refractory settings. In the TOURMALINE-MM1 study, ixazomib was added to the Rd backbone, demonstrating a superior medial PFS of 20.6 months as opposed to 14.7 months.[59] However, the statistical difference has not been demonstrated in the older age group.

The potential role of isatuximab, an anti-CD38 monoclonal antibody, was supported by the ICARiA-MM study when it was used in conjunction with pomalidomide and dexamethasone.[60] A significant proportion (65%) of the participants who received the intervention were aged ≥65 years. Overall, this resulted in a median PFS of 11.53 months compared with 6.47 months in the control.[60]

There are reasonable data on daratumumab in the relapsed or refractory settings. The CASTOR study investigated the combination of daratumumab and bortezomib, showing potential benefits for those aged ≥65 years.[61] When used with lenalidomide and dexamethasone, it was efficacious in those aged 65–74 years but not those aged ≥75 years.[62] The CANDOR study investigated the combination of daratumumab and carfilzomib and found no PFS benefit in those aged >65 years, potentially because of its adverse effects.[63] The emerging data on daratumumab in the upfront setting may phase out its use in the relapsed or refractory settings.

Elotuzumab used in junction with lenalidomide and dexamethasone was evaluated in the ELOQUENT-2 trial.[64] Survival benefit had been shown in those aged ≥75 years. When used in conjunction with pomalidomide and dexamethasone, median PFS and OS were prolonged; however, this had not been observed in the older age group.[65]

Although chimeric antigen receptor T cells have emerged as a novel immune therapy for heavily pre-treated patients with myeloma, this has not been studied in the older patients. It is worth noting that pre-treatment lymphodepleting agents, such as cyclophosphamide or fludarabine, and dose-related effects, including cytokine release syndrome and neurotoxicity, may limit its use in those with pre-existing age-related organ dysfunction, comorbidities, or frailty.

Despite novel agents, treatments in the relapsed or refractory settings for older patients with myeloma were mostly based on subgroup analyses in the large clinical trials. These were not necessarily representative of the real-world clinical scenarios of a significant proportion of older patients, who were likely to be frailer and less likely to tolerate salvage treatment.

CONCLUSION

Myeloma is a chronic disease of older people, with poor survival outcomes and quality of life. Older and frail patients are less able to tolerate treatment and more likely to experience disease progression. Although recent data on the novel chemotherapy agents showed promising results, it remains vital to consider frailty status, treatment toxicity, and quality of life when deciding on a management plan. In the authors' review, several validated frailty assessment tools can predict survival outcomes. However, their use in a clinical setting requires an extensive amount of expertise and time. The authors recommend screening older patients with simplified or performance-based tools at the first instance and, if resources permit, conducting a detailed frailty assessment. Fit, older patients with myeloma should be offered highly efficacious treatment regimens and considered for autologous stem cell transplant. Frail, older patients with myeloma should be offered a balanced approach. Moreover, continuous oral therapy such as lenalidomide

may be favoured over parenteral proteasome inhibitors. Dose reduction should be considered if toxicity limits treatment tolerability as there is emerging evidence of highly efficacious dose-reduced regimens. Early palliative care involvement and supportive measures form important aspects in managing older patients with myeloma but they are outside the scope of this review.

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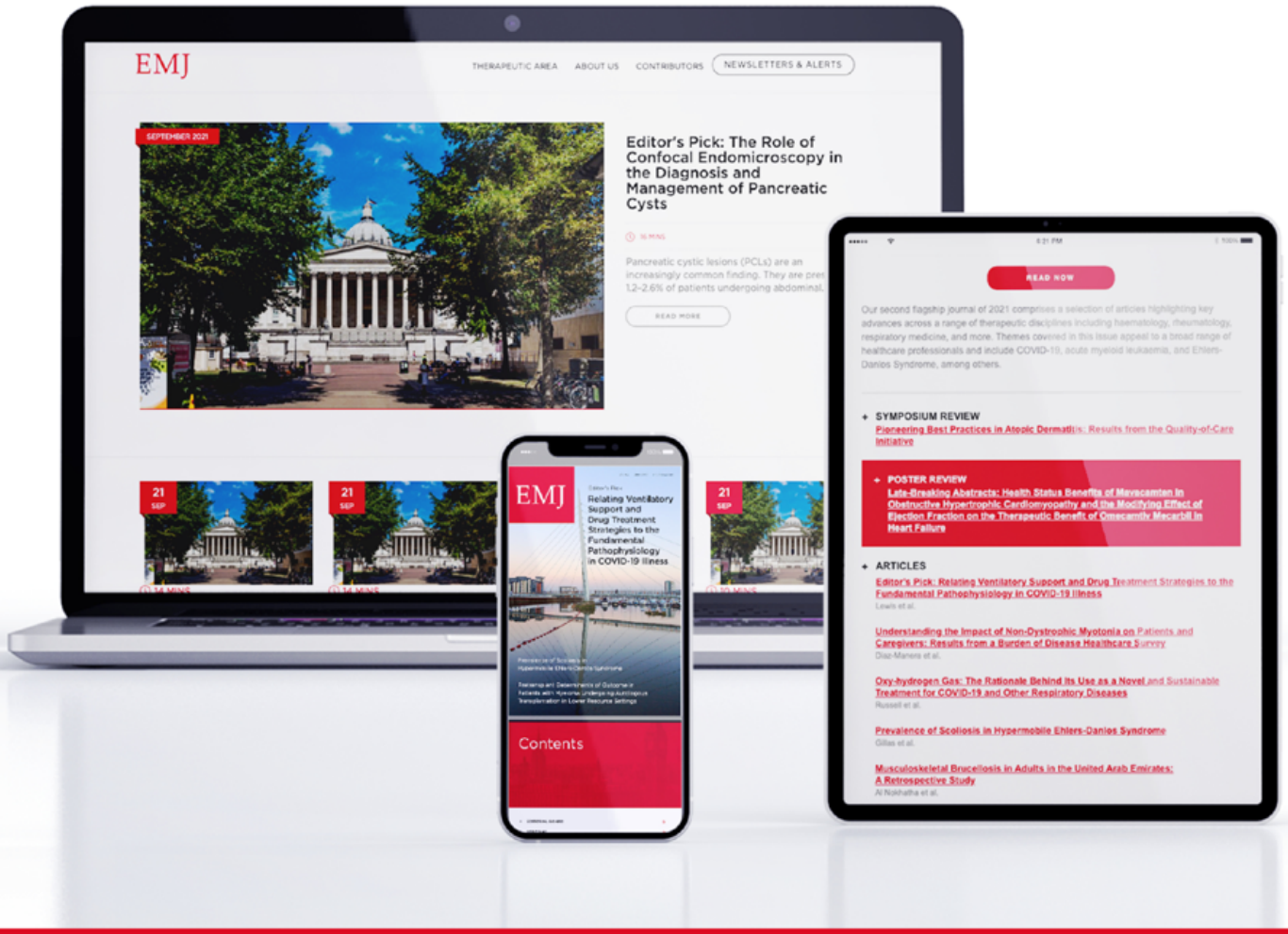

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Isatuximab and Belantamab Mafodotin: A Primer to an Evolving Multiple Myeloma Landscape

Authors: *Rebecca Gonzalez,[1,2] Hanna Bailey,[1,2] Omar Castaneda Puglianini[3]

1. Department of Pharmacy, Moffitt Cancer Center, Tampa, Florida, USA
2. Department of Blood and Marrow Transplant and Cellular Immunotherapy, Moffitt Cancer Center, Tampa, Florida, USA
3. Cellular Immunotherapies and Transplant Program, Division of Hematology/Oncology and Palliative Care, Virginia Commonwealth University, Massey Cancer Center, Richmond, Virginia, USA

*Correspondence to rebecca.gonzalez@moffitt.org

Disclosure: The authors have declared no conflicts of interest.

Received: 09.09.20

Accepted: 09.11.20

Keywords: B-cell maturation antigen (BCMA), Belantamab mafodotin, CD38, immunotherapy, isatuximab, monoclonal antibodies, multiple myeloma (MM).

Citation: EMJ Hematol. 2021; DOI/10.33590/emjhematol/20-00231.

Abstract

Multiple myeloma (MM) continues to be an incurable disease impacting mainly an ageing population. Comorbidities, disease characteristics, and drug toxicity profiles heavily influence treatment selections. Despite single agent activity of many anti-MM agents, opportunities to maintain responses most often include combination therapy with immunomodulator and/or proteasome inhibitor therapies. Monoclonal antibodies (moAb) have become an additional backbone to both newly diagnosed and relapsed or refractory transplant eligible and ineligible patients. Tolerability of these agents offers an additional benefit particularly to an ageing population. Two newly approved moAb targeting CD38 and B-cell maturation antigen have been added to the anti-MM arsenal. Isatuximab, a chimeric anti-CD38 moAb, is the second U.S. Food and Drug Administration (FDA)-approved CD38 targeted therapy offering unique mechanisms of action owing to differences in epitope binding and favourable side effect profiles. Belantamab mafodotin, a B-cell maturation antigen drug-antibody conjugate, is a first-in-class humanised moAb containing a distinct microtubule-disrupting agent: monomethyl auristatin-F. Its distinctive anti-MM activity includes antibody-dependent cellular cytotoxicity and phagocytosis, as well as direct cytotoxicity caused by internalisation of monomethyl auristatin-F. This review focusses primarily on the mechanisms of action, resistance patterns, and clinical utility of two recently FDA-approved agents; isatuximab in combination with pomalidomide and dexamethasone for relapsed or refractory MM exposed to at least two or more lines of therapy, and belantamab mafodotin monotherapy in relapsed or refractory MM exposed to four or more lines of therapy.

INTRODUCTION

As the second most common haematological malignancy, multiple myeloma (MM), a plasma cell disorder, continues to affect a significant portion of patients with increasing incidence over the past 25 years.[1-3] MM remains an incurable disease despite the continued improvement of outcomes over the past decades with immunomodulatory (IMID) and proteosome inhibitor (PI) therapies. Targeted immunotherapy with monoclonal antibodies (moAb) is critical for the successful treatment of different malignancies and is no different in MM. The first-in-class, humanised IgG1-κ moAb daratumumab targets the CD38 epitope and has rapidly changed the treatment landscape of MM, moving quickly from the relapsed or refractory to the upfront setting with unparalleled results.[4-6]

Several anti-CD38 and B-cell maturation antigen (BCMA) therapies are being developed for the treatment of MM.[7] Reflecting this rapid progress of MM drug development, two new agents received approval from the U.S. Food and Drug Administration (FDA): belantamab mafodotin, a monotherapy BCMA-directed antibody and microtubule inhibitor conjugate, and isatuximab, a CD38-directed cytolytic antibody, in combination with pomalidomide and dexamethasone. Studies have shown that these therapies are effective in the treatment of relapsed or refractory MM (RRMM) and are well tolerated with manageable side effects.[8,9]

This review specifically focusses on isatuximab and belantamab mafodotin including discussion of the mechanisms of action, clinical trial development leading to FDA approval, clinical activity, relevant adverse events (AE), as well as the manner in which these two agents are used within the MM treatment landscape. There is also a brief discussion of emerging moAb for the management of MM.

CD38 MONOCLONAL ANTIBODIES: ONE TARGET, MANY ACTIONS

Immunotherapy for the treatment of MM has become a significant addition to the anti-myeloma repertoire. CD38, a Type II transmembrane glycoprotein with ectoenzyme properties, has a prominent role in proliferation and growth of MM cells.[10,11] CD38 directed moAb offer a unique target because of its higher presence on MM and plasma cells, while having low expression on other myeloid and lymphoid cells, making it an ideal anti-MM therapy candidate.[2] Several mechanisms of anti-CD38 activity have been shown and are dependent on fragment crystallisable (Fc)-based immune activation. These include complement-dependent cytotoxicity (CDC), antibody-dependent cellular cytotoxicity (ADCC), and antibody-dependent cellular phagocytosis (ADCP), as well as direct apoptosis. CD38 moAb additionally offer immunomodulatory effects by way of regulatory and suppressor cell reduction and improved antitumour activity (Figure 1A).[12-14]

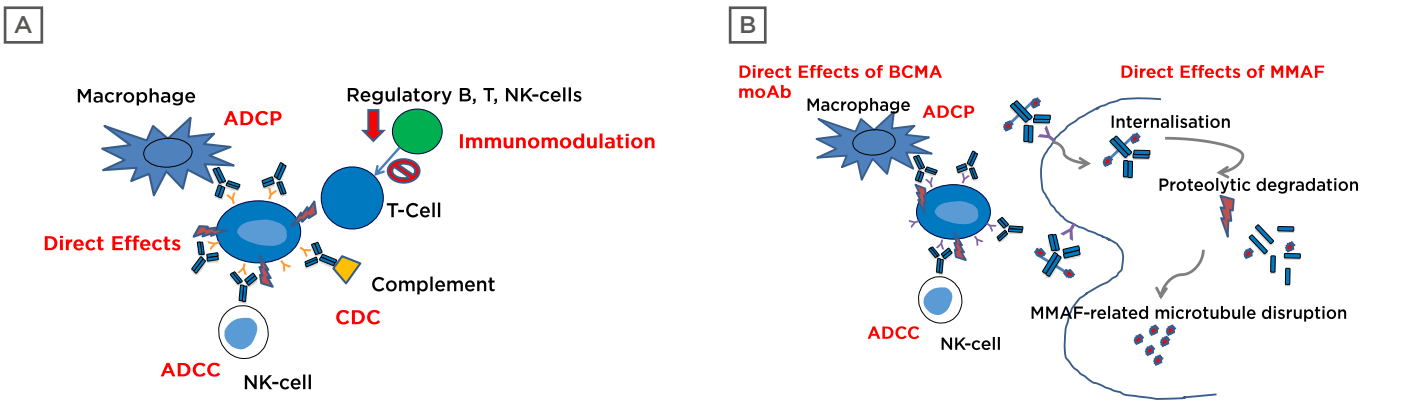

Figure 1: A) Anti-CD38 tumour kill mechanisms; B) belantamab mafodotin anti-multiple myeloma targets.

ADCC: antibody-dependent cellular cytotoxicity; ADCP: antibody-dependent cellular phagocytosis; BCMA: B-cell maturation antigen; CDC: complement-dependent cytotoxicity; MMAF: monomethyl auristatin-F; moAB: monoclonal antibody; NK: natural killer.

Differences among anti-CD38 moAb are highly dependent on the Fc-directed activity driven by location of epitope binding and subsequent anti-MM potency of the many immune mechanisms. There are currently four CD38 moAb therapies with Phase II or more clinical data (daratumumab, isatuximab, MOR,[15] and TAK-079[16]).[10,17]

Mechanisms and Resistance Methods

Effector cells, particularly natural killer (NK) cells are a crucial player in ADCC, whereas monocytes and macrophages are integral in ADCP-mediated cell killing and are the drivers at the forefront of anti-CD 38 moAb activity. Complement-driven activation increases recruitment of other immune cells and phagocytosis, while reducing inhibitory immune effector cells. Unlike other anti-CD38 moAb, daratumumab exhibits stronger CDC-driven activity over all other anti-MM mechanisms.[13] Direct anti-MM properties are highly variable among CD38 moAb and are dependent upon the ability to trigger apoptosis without Fc-driven binding. Daratumumab, unlike isatuximab, requires secondary cross-linking to induce programmed cell death, whereas isatuximab independently induces reactive oxygen species and liposomal-mediated death.[10,13] Suppression of regulatory cells, including T and B cells, leads to improved effector (T and NK) cell numbers and activity while promoting an anti-MM microenvironment.[12,13]

Eventually patients with MM exposed to CD38 directed therapy will progress; however, several resistance mechanisms, both primary and acquired, are known and strategies to overcome this barrier are expanding.[12] Concerns over prior therapy exposure, disease cytogenetics, and reintroduction of prior refractory agents are some patient-specific factors to consider.[12] In a study conducted by Nijhof et al.,[18] evaluation of Fc-dependent mechanisms of daratumumab showed heterogeneous CD38 expression, but similar activity of ADCC and CDC among newly diagnosed MM (NDMM) and RRMM patients, indicated that refractoriness to other anti-MM agents did not confer similar refractory response with CD38 moAb.[18] Utilisation of anti-CD38 therapy in smouldering MM (SMM) showed higher single-agent daratumumab response-rates compared to heavily pretreated MM patients, leading the authors to note potential variations in the tumour microenvironment and immune impairment with disease progression.[19]

Single-agent activity of anti-CD38 therapies is evident; however, durability of response is limited. Combination of anti-MM therapy (PI or IMID) is one possible mechanism to boost activity and potentially overcome resistance. Synergistic activity of IMID therapy to augment immune effector cell activity and enhance anti-CD38 therapy has been shown in patients who were previously refractory to one or both therapies.[20-23] Additionally, high-risk cytogenetic features such as t(4;14), t(4;16), and del17p continue to negatively impact overall response and survival of patients with MM. Anti-CD38 moAb therapy unfortunately does not abrogate inferior responses in high-risk patients.[12,21,24]

Additional resistance to CD38 moAb therapy may develop as a result of loss of CD38 cell surface density expression and/or increase in soluble CD38, leading to reduced ADCC, ADCP, and CDC capabilities.[10,13] Susceptibility to these killing methods is heavily driven by cell surface expression; methods to increase surface density with all-trans retinoic acid,[18] panobinostat,[25] and IMID therapies have been proven to upregulate CD38 expression.[12] Upon administration of daratumumab, a significant reduction in CD38 density expression from direct cell surface loss has been previously noted, regardless of treatment response.[11,13] This reduction can be transient as baseline levels have been restored up to 6 months postexposure.[18] This phenomenon is not noted with isatuximab therapy, although an increase in CD38 internalisation has been reported, this property is potentially driven by a different epitope binding site.[10] Other drivers of resistance may include complement inhibitory proteins, anti-apoptotic proteins such as survivin, reduction in NK-cell numbers, and Fc-receptor polymorphisms.[13]

ISATUXIMAB: EXPANSION OF CD38 TARGETING

Unlike other CD38 moAb therapies, isatuximab's epitope binding on CD38 is located away from catalytic activity site, uniquely increasing its inhibition of enzymatic activity and contributing to its variances in mechanism of action.[10] Isatuximab's main anti-MM kill mechanism is through ADCC, which can be enhanced through concurrent use of both PI and IMID therapies. Demonstrations of enhancement in direct cytotoxicity and cell lysis have been shown

with combined therapies versus single-agent isatuximab; although, isatuximab does exhibit a dose-dependent CD38 enzymatic inhibition more potent than daratumumab.[10,26] During initial monotherapy dose-escalation trials, isatuximab was given intravenously to RRMM patients at dosages up to 20 mg/kg weekly or every 2 weeks. The maximum tolerated dose was not reached because of lack of significant AE. The most common AE was infusion-related reactions (IRR) occurring in 49.3% patients, with mandatory prophylaxis given at dose levels more than 3 mg/kg. Symptoms included shortness of breath, nausea, headache, chest discomfort, and pyrexia. Most often, IRR occurred within first infusion and was associated with CDC activity. Haematologic toxicity occurred in 45–98% of patients, while fatigue and nausea occurred in approximately 35%.[27] A Phase II dose-escalation trial[28] supported isatuximab clinical and pharmacokinetic activity and determined the single-agent dosing strategy of 20 mg/kg weekly for four doses, followed by 20 mg/kg every 2 weeks. When combined with dexamethasone 40 mg or 20 mg daily in patients aged >75 years, isatuximab combination therapy had significant improvements in overall response rate (ORR), median progression-free survival (PFS), and reduction in IRR.[29]

Synergistic activity with other anti-MM therapies has proven effective throughout the history of MM treatment. Due to several MM subclones and the heterogeneity of the disease, combination strategies with IMID and PI have been effective with daratumumab and now isatuximab.[26] Isatuximab combination with other IMID, such as lenalidomide, established a lower dosing strategy of four weekly doses of 10 mg/kg followed by doses every 2 weeks because of similar outcomes but higher Grade ≥3 toxicities noted with higher dosing.[21] Most recently, isatuximab was studied in a Phase II trial[24] combining pomalidomide in patients with lenalidomide and PI refractory disease (82% and 84%, respectively). These results led to a Phase III, prospective trial (ICARIA-MM)[8] of isatuximab with and without pomalidomide and dexamethasone in RRMM patients. Triple therapy in highly refractory patients improved PFS regardless of age (>75 years),[30] renal impairment,[31] high-risk cytogenetics,[32] or those with more than three prior lines of therapy[33] or dual-refractory disease. Minimal residual disease negativity (level of 10^{-5}) was also obtained in 5% of triple therapy patients versus none in doublet combination patients. Neutropenia and infections remained the most common AE among both treated groups with approximately 40% (Grade 3–4: 2.6%) experiencing isatuximab-IRR.[8] Outcomes from the ICARIA trial[8] led to FDA approval of isatuximab[34] on 2nd March 2020. Clinical discussion of the major isatuximab trials is summarised in Table 1. [8,21,24,27,28]

Additional activity was also noted with a PI in a Phase Ib trial of isatuximab with carfilzomib and dexamethasone. When given together with biweekly carfilzomib, isatuximab had an ORR of 60.6% in patients who had received prior carfilzomib (45.0%) and were dual-refractory (79.0%).[35] Similar to the ICARIA clinical trial, the IKEMA study is prospectively evaluating isatuximab with and without carfilzomib and dexamethasone.[36] Results of this trial will further add to the understanding of standard doublet-therapy versus triple-therapy in RRMM patients, especially amongst those with dual-refractory disease.

CLINICAL TRIALS AND FUTURE OPPORTUNITIES

Opportunities to improve patient care experiences with different CD38 moAb include recent approval of subcutaneous daratumumab administration,[37] isatuximab fixed-volume infusions reducing infusion duration to less than 2 hours,[38] reduced IRR moAb MOR-202,[15] and nonhyaluronidase-containing subcutaneous formulation of TAK-079.[16] Due to its efficacy and tolerability in the RRMM setting, there are several ongoing clinical trials investigating the efficacy of isatuximab in combination with both IMID and PI therapies in patients with NDMM. These include both transplant eligible[39] and transplant ineligible[40-43] patients. Additionally, isatuximab is currently being investigated as a monotherapy in SMM.[10,26] Utilising CD38 moAb therapy earlier on may benefit from a more 'fit' immune system for modulation; however, exact sequence of use and corresponding resistance patterns are still being questioned.

Concerns regarding emergence of CD38 moAb therapies in both SMM and NDMM patients may change these responses in RRMM patients, however, full understanding

has yet to be elucidated. Additionally, with different mechanisms of action and epitope binding properties, isatuximab may be useful in previously exposed daratumumab patients. Gandhi and colleagues[23] reported on the extent of success of anti-CD38 therapy in 275 patients with refractory CD38 disease. This retrospective study (MAMMOTH) analysed triple-, quadruple-, and penta-refractory patients exposed to daratumumab (93%) and isatuximab (7%). Survival was significantly affected by level of refractoriness to anti-MM therapies. Patients who were penta-refractory had approximately 5.0 months less survival compared with nontriple-refractory (11.2 months) and those refractory to CD38 moAb had an overall survival (OS) of 8.6 months. A Phase I trial[44] of isatuximab monotherapy in patients with prior daratumumab exposure was ongoing at the time of writing.

Clinical responses with anti-CD38 therapies are promising; however, due to small numbers of high-risk patients in clinical trials (20% approximately in monotherapy[27] and ICARIA-MM[8]), it is not fully clear if anti-CD38 therapies can mitigate these oncogenic impacts on durability of response.[27] A trial[45] is currently investigating the role of isatuximab monotherapy in high-risk SMM patients and may offer further insight into the role of targeted therapies in modifications of patient-specific therapy based on mutations, molecular characteristics, and minimal residual disease status,[14] and may also offer insight into the particular role of CD38 moAb therapy to obtain deeper and better responses.

Table 1: Isatuximab clinical trials in relapsed or refractory multiple myeloma patients.[8,21,24,27,28]

	Phase	N	Number of prior treatment lines (median, range)	ORR (%)	PFS (median, months)	DOR	AE
Isa mono[27]	I (dose expansion phase)	84	5 (1–13)	>10 mg/kg: 23.8 High-risk: 16.7	>10 mg/kg: 3.7 >10 mg/kg + high-risk: 2.9	Low risk: 37 W high-risk: 25 W	51% IRR
Isa mono[28]	II	97	5 (2–14)	10 mg/kg · Q2/Q4W: 20 · Q2: 29.2 20 mg/kg · QW/Q2W: 24	>10 mg/kg (n=18/74): 4.6	10 mg/kg · Q2/Q4: 8.3 · Q2: 14.8 20 mg/kg QW/Q2W: 8.3	51.5% IRR; Grade ≥3: cytopenias; PNA
Isa-RD[21]	Ib	57	5 (1–12)	56 (n=26/52)	8.5	10.9 months	Grade 3 PNA (n=1); 56% IRR
Isa-PD[24]	Ib	45	3 (1–10)	62	17.6	18.7 months	Grade ≥3: PNA; haematologic 42% IRR
Isa-PD versus PD[8]	III	154 Isa-PD versus 153 PD	3 (2–4)	60 Isa-PD versus 35 PD	11.5 Isa-PD versus 6.5 PD High-risk versus standard-risk HR similar	13.3 months Isa-PD versus 11.1 months	URI (28% Isa-PD versus 17%); diarrhoea (26% Isa-PD versus 20% PD); 38% IRR

AE: adverse event; D: dexamethasone; DOR: duration of response; HR: hazard ratio; IRR: infusion-related reactions; Isa: isatuximab; mono: monotherapy; ORR: overall response rate; PD: pomalidomide and dexamethasone; PFS: progression-free survival; PNA: pneumonia; Q: every; R: lenalidomide; URI: upper respiratory infection; W: weeks.

B-cell Maturation Antigen: A New Versatile Target

Despite significant advances in MM treatment, many patients develop resistance or intolerance to available therapeutics including PI, IMID, and anti-CD38 moAbs. In the last few years, BCMA has emerged as an appealing target in MM because it is almost exclusively expressed on mature B-lymphocytes, plasma cells, and MM cells. BCMA belongs to the TNF receptor superfamily and is critical for bone marrow plasma cell long-term survival.[46] Serum BCMA concentrations have been shown to be elevated in patients diagnosed with MM compared with healthy controls and patients with more progressive disease as opposed to those responding to treatment.[47,48] These observations have led to various treatment modalities being investigated targeting BCMA, including antibody drug conjugates (ADC), chimeric antigen receptor T cells (CAR-T), and T-cell engaging bispecific antibodies.[49] For the purpose of this review, advances in ADC therapies targeting BCMA will be outlined with a focus on the recently FDA-approved belantamab mafodotin.

Belantamab Mafodotin: One More Card to Play

Belantamab mafodotin has a multimodal activity against MM cell lines (Figure 1B). It is a humanised, afucosylated IgG1 anti-BCMA moAb connected by a protease-resistant linker to monomethyl auristatin-F (MMAF), a microtubule polymerisation inhibitor. Upon binding to BCMA, belantamab mafodotin is rapidly internalised, releasing its MMAF toxic payload and triggering cell cycle arrest in the G2/M phase that is followed by apoptosis.[50] In addition, the afucosylation of Fc tail increases binding affinity of belantamab mafodotin to FcγRIIIa receptors present on target cells leading to ADCC and ADCP.[51]

Based on promising preclinical data, belantamab mafodotin was evaluated in a dose-escalation and expansion Phase I DREAMM-1 study in RRMM patients who received prior treatment with alkylators, PI, and IMID, and were resistant to the latest line of therapy.[52,53] In the dose-expansion phase, ORR was 60%, including: two patients (6%) with stringent complete response; three patients (9%) with complete response; 14 patients (40%) with very good partial response (VGPR); and two patients (6%) with partial response. Median time to response was 1.2 months, with responses deepening with time. Median PFS was noted to be 12.0 months with a median duration of response (DOR) of 14.3 months. Of significance, median PFS of 6.2 months was much lower in patients who had received prior daratumumab therapy and were refractory to PI and IMID. Grade 3 or 4 AE were observed in 83% of patients including thrombocytopenia (35%) and anaemia (17%). Corneal toxicity, both keratopathy and visual acuity changes, occurred in 69% of patients and was likely related to the direct effects of MMAF-related toxicity. Twenty-nine percent of patients experienced IRR, the majority of them being mild in severity and occurred with first dose. Recently, Lonial and colleagues[9] published the results of the DREAMM-2 study, a two-arm open-label randomised Phase II trial that evaluated belantamab mafodotin 2.5 mg/kg versus 3.4 mg/kg given intravenously every 3 weeks in RRMM patients who had received at least three prior lines of therapy and were refractory to PI and IMID, and refractory or intolerant to anti-CD38 moAb. ORR was 31% in the 2.5 mg/kg arm versus 34% in the 3.4 mg/kg arm with at least VGPR observed in 19% and 20%, respectively. The median PFS reported was 2.9 months in the 2.5 mg/kg group versus 4.9 months in the 3.4 mg/kg arm. The median DOR and OS data are not mature to date. The most common Grade 3 or 4 AE were keratopathy (27% in 2.5 mg/kg versus 21% in 3.4 mg/kg), thrombocytopenia (20% versus 33%, respectively), and anaemia (20% versus 25%, respectively). The findings of the dose-expansion part of DREAMM-1 and DREAMM-2 trials are summarised in Table 2.[9,52,53]

DREAMM-2 trial outcomes in patients with high-risk cytogenetics including t(4;14), t(14;16), 17p13del, or 1q21+ have been reported separately.[54] High-risk cytogenetics were observed in 42% of patients in the 2.5 mg/kg group and 47% of patients in the 3.4 mg/kg group. ORR was reported in 27% (22% with ≥VGPR) in the 2.5 mg/kg group and 40% (27% with ≥VGPR) in the 3.5 mg/kg group. Median PFS was 2.1 months versus 5.8 months, respectively, and median OS was 9.4 months versus 13.8 months.

Table 2: Belantamab mafodotin clinical trials with relapsed or refractory multiple myeloma patients.[9,52,53]

Trial	Phase	N	Number of prior treatment lines	ORR (%)	Median PFS (months)	Median DOR (months)	AE (all grades)
DREAMM -1[52,53]	I (dose expansion phase)	35	≥5: 57% (1–10 range)	60	12	14.3	69% corneal toxicity; 63% TCP; 29% IRR
DREAMM -2[9]	II	97 (2.5 mg/kg) versus 99 (3.4 mg/kg)	>4: 84% (2.5 mg/kg) versus 83% (3.4 mg/kg)	31 (2.5 mg/kg) versus 34 (3.4 mg/kg)	2.9 (2.5 mg/kg) versus 4.9 (3.4 mg/kg)	NR Both	2.5 mg/kg: 70% corneal toxicity; 35% TCP; 21% IRR 3.4 mg/kg: 75% corneal toxicity; 58% TCP; 16% IRR

AE: adverse event; DOR: duration of response; IRR: infusion-related; NR: not reached; ORR: overall response rate; reaction; PFS: progression-free survival; TCP: thrombocytopenia.

These results seem to suggest that belantamab mafodotin has similar activity in high-risk RRMM patients compared to the general RRMM population.

Following the results of DREAMM-2, belantamab mafodotin received FDA approval on 5th August 2020. Although it demonstrated an acceptable toxicity profile, belantamab mafodotin administration will be required through a risk evaluation and mitigation strategy programme due to the significant risk of ocular toxicity.[55] This programme requires patients to undergo ophthalmic examinations (slit lamp and visual acuity) at baseline and prior to each dose. Even though prophylactic use of steroid eye drops seemed to provide no benefit to prevent the development of corneal AE in DREAMM-2,[9,56,57] patients were advised to use preservative-free lubricant eye drops during treatment. General management of corneal toxicity consists of dose modifications and interruptions in therapy as described in the DREAMM trials, with the median time to keratopathy resolution being 2 months and visual acuity changes at 22 days.

Resistance Mechanisms

Anti-BCMA therapeutic efficacy as well as DOR may be contingent on the levels of soluble BCMA (sBCMA). This formation occurs as a result of BCMA shedding from the cell surface because of the direct cleavage by ubiquitous γ-secretase.[58] It has been previously described that sBCMA prevent anti-BCMA antibody activity through competitive binding and serving as a soluble decoy for antibodies.[59] Clinically, increased blood levels of sBCMA have been associated with progression of disease and shorter OS.[47] The use of γ-secretase inhibitors to overcome resistance and increase anti-BCMA activity has been previously described in CAR-T therapy *in vivo*[60] and in combination with belantamab mafodotin *in vitro*.[61] A Phase I/II trial will evaluate the efficacy and safety of belantamab mafodotin in combination with a γ-secretase inhibitor, nirogacestat (DREAMM-5).[62]

Another way to combat resistance to anti-BCMA treatment is to design therapeutic agents with preferential binding affinity to membrane-bound BCMA versus sBCMA. MEDI2228 is a fully human ADC connected to a pyrrolobenzodiazepine payload, which induces DNA damage and apoptosis following internalisation. Preclinical

data suggest that MEDI2228 may display weak binding to sBCMA compared to membrane-bound BCMA, as well as more potent activity to prevent MM cell proliferation and survival compared with MMAF.[63,64] A Phase I study is currently enrolling patients with RRMM to evaluate the dosing and safety of MEDI2228.[65]

FUTURE DIRECTIONS

Due to its significant single-agent activity in MM, belantamab mafodotin is being evaluated in various combination regimens as part of a series of DREAMM trials. Two Phase I/II trials will assess the combination of belantamab mafodotin with pomalidomide and dexamethasone[66] or pembrolizumab (DREAMM-4).[67] Early results of a Phase I/II trial evaluating belantamab mafodotin in combination with dexamethasone and bortezomib or lenalidomide reported 78% ORR and 50% at least VGPR in a bortezomib-containing arm (DREAMM-6).[68] Bortezomib and dexamethasone in combination with belantamab mafodotin or daratumumab will be studied in a Phase III trial (DREAMM-7).[69] Another Phase III trial will assess belantamab mafodotin, pomalidomide, and dexamethasone combination versus bortezomib, pomalidomide, and dexamethasone (DREAMM-8).[70] Finally, belantamab mafodotin in combination with triplet therapy consisting of bortezomib, lenalidomide, and dexamethasone will be compared with triplet therapy alone in a Phase III study of transplant ineligible NDMM patients (DREAMM-9).[71]

With multiple anti-BCMA treatment options being evaluated and nearing FDA approval, including CAR-T cell therapy and T-cell engaging bispecific antibodies, one of the most important questions will be the choice of specific anti-BCMA treatment. ADC, such as belantamab mafodotin, may provide an advantage due to its relatively simplified manufacturing process and immediate availability compared to CAR-T. In addition, ADC may be better suited in those patients who are frail as it carries no risk of cytokine release syndrome seen with other anti-BCMA treatment modalities. One of the other considerations is that BCMA expression may be preserved at disease progression allowing for different anti-BCMA therapy following relapse.[72] At this time, specific successive treatment patterns for various BCMA-targeted therapies remains to be elucidated.

CONCLUSION

Evolution of MM treatment has rapidly expanded over the past 5 years, offering unique biologic targeting focussing on immunotherapeutic mechanisms to control disease progression and providing deeper and durable responses. While the most effective treatment sequence for both newly diagnosed and refractory patients has yet to be determined, these two agents offer additional therapeutic options for tailoring patient care. Strategies for selection of therapies based upon cytogenetic risk will certainly be a major driver in the MM treatment landscape and both isatuximab and belantamab mafodotin are currently being investigated in this arena. Unique triple and quadruple combinations with BCMA and CD38 moAb may offer transplant-ineligible patients desirable outcomes with a lower risk of disease progression and improved OS without compromising tolerability. In transplant-eligible patients, the ability to achieve a better disease control may allow for improved transplant-related outcomes. Finally, the approval of these agents has offered an additional lifeline to RRMM patients.

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Current and Future Therapies for β-Thalassaemia: A Review Article

Authors: Livia Giannoni, *Emanuele Angelucci

Haematology and Transplant Unit, IRCCS Ospedale Policlinico San Martino, Genova, Italy
*Correspondence to emanuele.angelucci@hsanmartino.it

Disclosure: The authors have declared no conflicts of interest.

Received: 15.10.20

Accepted: 04.03.21

Keywords: Gene therapy, haemopoietic cell transplantation (HCT), iron chelation, iron metabolism, transfusion-dependent thalassaemia (TDT).

Citation: EMJ Hematol. 2021;9[1]:94-104.

Abstract

This article will review recent and forthcoming advances in the treatment of thalassaemia. Prognosis of thalassaemia has dramatically improved in the last 50 years with the development of regular and safe blood transfusions and iron chelation. Almost 20 years ago, development of oral chelators, and more recently the improvement in the knowledge and understanding of iron pathophysiology, have led to optimal iron toxicity prevention and treatment. These considerable advancements in medical therapy have transformed transfusion-dependent thalassaemia from a lethal childhood disease to a chronic disease with an open prognosis, even in those individuals over 50 years of age, and with the disease being, in some instances, curable. In the 1980s, the introduction of allogeneic haematopoietic cell transplantation provided the possibility of curing the congenital disease for the first time. More recent developments include an improved understanding of erythropoiesis, which led to the development of new erythroid-stimulating factors effective in thalassaemia, an expansion of donor pull for transplantation, and the approach of the long-term promised gene therapy in clinical practice. Moreover, ongoing trials of gene editing and agents modulating iron metabolism promise new improvements. Today, patients with thalassaemia have several weapons in their therapeutic arsenal and, hopefully, will have much more to come. As usual in medical practice, new advancements provide new challenges for the medical community, and it is the duty of this community to clearly understand the benefits and challenges of any new approach in order to provide the highest clinical benefit to patients.

INTRODUCTION

β-thalassaemias are a clinically heterogenous group of inherited disorders caused by >200 described mutations in the β-globin gene, leading to a decreased or absent production of the β-globin chain. The hallmark of the disease is the imbalance in the α/β-globin chain production, which results in variable grades of ineffective erythropoiesis for apoptosis of late-stage erythroid precursors, chronic haemolytic anaemia, compensatory haemopoietic expansion, hypercoagulability, and increased iron absorption.[1] Approximately 1.5% of the global population are carriers for a β-thalassaemia mutation, with traditionally higher prevalence in populations where malaria

is or was endemic such as the Middle East, the Mediterranean region, and Southeast Asia;[2] however, prevention programmes and migrations have recently contributed to a change in the pattern of thalassaemia distribution worldwide.[3] Improved public health measures have prolonged life expectancy of affected individuals in low- and middle-income countries, making β-thalassaemia a significant global health problem.[4]

Current guidelines have adopted a clinical classification of thalassaemia syndromes based on the magnitude and frequency of transfusion requirements, which are considered to reflect the severity of the disease.[5,6] Patients with transfusion-dependent thalassaemia (TDT) present with severe anaemia as early as 6 months of age and require life-long blood transfusion to survive.[1] Conversely, in non-transfusion-dependent thalassaemia (NTDT), patients usually maintain haemoglobin (Hb) levels between 7 and 10 g/dL and may require transfusions sporadically. They eventually develop clinically significant iron overload, mainly as a consequence of erythron expansion and increased duodenal iron absorption driven by hepcidin suppression.[7] This review aims to provide a summary of the current and emerging treatment strategies for β-thalassaemia.

CURRENT TREATMENTS (STANDARD THERAPY)

Transfusion and Chelation

The aim of red blood cell transfusion in thalassaemia is to restore normal Hb values and to suppress ineffective erythropoiesis, thus attenuating the downstream consequences.[1] In chronically transfused patients with TDT, the transfusion-mediated rise in Hb suppresses erythropoiesis and is associated with a rise in hepcidin levels.[8] Improvements in blood product administration practices and more effective iron chelation were associated with better survival outcomes and fewer cardiac complications.[9] The best course of action to suppress abnormal erythropoiesis, minimise iron overload, guarantee normal growth, and avoid hyperviscosity contemplates a pre-transfusion level between 9 and 10.5 g/dL, with a higher target of 11–12 g/dL for patients with cardiac involvement or with extramedullary pseudotumours.[10] Conversely, in NTDT, transfusion may be indicated sporadically or for temporary periods in specific situations;[7] clear evidence regarding the most appropriate target of pre-transfusion Hb in NTDT is lacking and some patients, specifically those with the HbE/β-thalassaemia genotype, seem to be able to adapt to lower Hb levels.[11] Patients with NTDT placed on transfusion regimens seem to have fewer complications deriving from chronic anaemia and ineffective erythropoiesis (extramedullary haematopoiesis, pulmonary hypertension, thrombotic events);[12] on the other hand, given the increased risk of alloimmunisation and particularly of secondary iron overload under chronic transfusion regimens, the decision to commit to a regular transfusion programme must be well thought-out and patients must be evaluated a long time before/after acute episodes.[7]

In TDT, transfusion iron can accumulate at a rate of 0.3–0.6 mg/kg with a standard chronic transfusion regimen; iron from senescent red blood cells is stored mainly by reticuloendothelial macrophages and rapidly released into the plasma, where transferrin is saturated and labile toxic iron species emerge.[13] The most important advancement in iron chelation treatment has been the understanding that iron tissue toxicity is not only related to iron overload but to the presence of toxic iron species in the plasma.[14] Therefore, iron chelation therapy (ICT) is administered with the primary goal of removing iron oxidative species emerging in the plasma after transferrin saturation, and the secondary goal of removing formerly deposited iron. An iron overload assessment is thus recommended as soon as 10 units of red blood cells have been transfused, through liver iron concentration (LIC) measurement by MRI or, if not applicable or unavailable due to limited resources, through serum ferritin level measurement. For TDT, a threshold of >1,000 ng/mL is usually an indication for ICT requirement and a value >2,500 ng/mL strongly correlates with cardiac siderosis and endocrinopathy.[15]

In NTDT, iron overload is related to increased intestinal absorption secondary to suppressed hepcidin. Hepcidin is synthesised in the liver and promotes degradation of ferroportin, the only known cellular iron exporter expressed on

macrophages, hepatocytes, and on the basolateral membrane of enterocytes, thus reducing iron absorption.[14] Ineffective erythropoiesis and erythroid expansion have been suggested to promote suppression of hepcidin, despite the onset of iron overload, through production of the erythroblast-derived factor erythroferrone.[16] This results in a slower rate of iron accumulation in NTDT compared to TDT and in a different distribution, with slower or absent myocardial involvement even in the presence of elevated LIC.[17] Guidelines recommend ICT if LIC is >5 mg iron/g dry weight or serum ferritin is >800 ng/mL, although more recent data showed significant iron overload for ferritin values in the 300–800 ng/mL range.[18]

Three iron chelators are licensed by most regulatory agencies for thalassaemia (deferoxamine [DFO], deferasirox, and deferiprone) and the choice should be carefully evaluated by clinicians. DFO was the first available chelator and is administered parenterally, subcutaneously, or intravenously; it has a short half-life of only 20–30 minutes and needs to be administered as a continuous infusion of 12 hours for 5–7 days per week, thus making it a less attractive choice for non-compliant patients. Despite the introduction of oral iron chelators, DFO is still considered the first-line choice in paediatric patients with TDT under the age of 6 years in Europe and for all patients with TDT in low-income countries due to lower costs. Deferasirox monotherapy at a dose of 20–40 mg/kg once daily proved effective as a first-line therapy for transfusional iron overload in TDT for reducing serum ferritin and LIC and ameliorating myocardial T2* on MRI, even in heavily iron-overloaded patients.[19,20] Deferasirox is also the only iron chelator evaluated in a randomised clinical trial in NTDT, showing efficacy in reducing LIC in patients ≥10 years of age with a baseline value of at least 5 mg iron/kg dry weight.[21] Deferiprone is an oral (administration 3 times per day) absorbed iron chelator licensed in most countries as a second-line therapy for iron overload in patients with TDT >6 years of age. Its efficacy in LIC reduction has also largely been demonstrated.[22] Sporadic severe cases of granulocytopenia have been reported. Notably, a combination therapy of DFO and deferiprone proved effective in the management of cardiac overload, by ameliorating cardiac T2* on MRI and left ventricular ejection fraction.[23]

Allogeneic Haemopoietic Cell Transplantation

The rationale for haematopoietic cell transplantation (HCT) in thalassaemia is to replace ineffective endogenous erythropoiesis and to correct the phenotypic expression of the disease, sparing patients from life-long transfusion treatment and long-term complications.[24] HCT is, so far, the only consolidated approach with a curative potential in TDT. Transplantation in TDT is now performed worldwide with excellent results.[25-28] The latest report from The European Society for Blood and Marrow Transplantation (EBMT) Registry showed a global overall survival (OS) and event-free survival (EFS) of 88% and 81%, respectively, with best results obtained in patients ≤14 years of age (OS and EFS of 90% and 83%, respectively).[29] Current recommendations identify young patients with TDT, before development of iron-related organ damage, as the ideal candidates for HCT;[30] adults can also be offered this strategy in the setting of dedicated programmes, provided that they have been well-chelated since infancy. According to the EBMT Registry data, better outcomes are still obtained from transplants with human leukocyte antigen (HLA)-matched siblings, with an OS of 91% and EFS of 83%.

The possibility of finding an HLA-matched sibling donor ranges from 60 to 70% in countries where families are larger and an average of 25–30% in western countries,[31] highlighting the need for alternatives. In the era of high-resolution HLA typing, transplantation from matched unrelated donors in TDT is considered feasible and effective. Transplantation from alternative donors has resulted in conflicting results so far. Primary graft failure appears as the major complication of unrelated cord blood unit transplants, while the need to abate the risk of graft-versus-host disease has prompted the search for effective modalities of *ex vivo* or *in vivo* T-cell depletion with grafts from haploidentical donors. Recent reports of alternative HCT donors are summarised in Table 1.[32-38]

Table 1: Haematopoietic stem cell transplantation from alternative donors in patients with thalassaemia.

Study; number of patients	Donor	Manipulation	Conditioning	GVHD prophylaxis	Results (OS, TFS, GF)	Notes
Li et al.,[32] 2019; 355	MUD/MMUD	none	MAC Bu based	Various	OS: 87% MUD, 78% MMUD; TFS: 82% MUD, 78% MMUD; GF: 6% MUD, 11% MMUD	aGVHD 21% cGVHD 13%
Fleischauer et al.,[33] 2006; 72	MUD/ MMUD	none	Bu Cy Bu Cy TT Bu Flu TT	CsA+MTX ATG+CsA+ MTX (25%)	OS: NR; TFS: 76% HLA *DPB1* matched or permissive, 57% HLA *DPB1* non-permissive; GF: 10%	aGVHD 27%
Huang et al.,[34] 2018; 50	MUD/MMUD	none	Bu Cy Flu	ATG+CsA+ MTX	OS: 94%; TFS: 92%; GF: 0%	Median age: 4.6 years (range: 2–12 years)
Ruggeri et al.,[35] 2011; 35/51	Unrelated UCB	none	MAC 30/35	CsA-based 27/35	OS: 65%; TFS: 21%; GF: 52%	none
Jaing et al.,[36] 2012; 35	Unrelated UCB	none	Bu-Cy	ATG+CsA+ MP	OS: 88%; TFS: 74%; GF: 12%	none
Gaziev et al.,[37] 2018; 40	Haploidentical	CD3+/CD19+ depletion	Bu-TT-Cy (preceded by Flu)	ATG+CsA+ MP	OS: 78%; TFS: 39%; GF: 45%	none
Gaziev et al.,[37] 2018; 11/14	Haploidentical	αβ/CD19+ depletion	Bu-TT-Cy (preceded by HuAzFlu)	ATG + CsA+MP/ MMF	OS: 84%; TFS: 69%; GF: 14%	none
Anurathapan et al.,[38] 2020; 83	Haploidentical	none	ATG-Bu-Flu (preceded by DxmFluVelRit)	PT-Cy +tacrolimus/ sirolimus	OS: 96%; TFS: 96%; GF: NR	52 patients treated with the full pretransplant immunosuppression protocol engrafted uneventfully

aGVHD: Acute graft-versus-host disease; ATG: anti-thymocyte globulin; Az: azathioprine; Bu: busulfan; cGVHD: chronic graft-versus-host disease; CsA: cyclosporin A; Cy: cyclophosphamide; Dxm: dexamethasone; Flu: fludarabine; GF: graft failure; GVHD: graft-versus-host disease; HLA: human leukocyte antigen; Hu: hydroxyurea; MAC: myeloablative conditioning; MMF: mycophenolate mofetil; MMUD: mismatched unrelated donor; MP: methylprednisolone; MTX : methotrexate; MUD: matched unrelated donor; N/A: not applicable; NR: not reported; OS: overall survival; PT-Cy: post-transplant cyclophosphamide; Rit: rituximab; TFS: thalassaemia-free survival; TT: thiotepa; UCB: umbilical cord blood; Vel: velcade.

Erythroid Maturating Agents

Members of the TGF-β superfamily of ligands, including several bone morphogenetic proteins, growth-differentiation factors, and activins, have been known to be inhibitors of late-stage erythropoiesis. Their complex interaction with erythroid precursors was recently reviewed.[39] Activin receptor ligand traps (sotarcept and luspatercept) are fusion proteins that act as extracellular traps for a wide range of ligands of the TGF-β superfamily, thereby preventing receptor binding and stimulation of downstream signalling. This approach proved capable of correcting anaemia in an erythropoietin (EPO)-independent fashion in mouse models of ineffective erythropoiesis, thus raising interest surrounding its possible clinical application in thalassaemia or myelodysplastic syndromes.[40] The specific pathway inhibited by these drugs is still a matter of debate, with growth-differentiation factor-11 signalling primarily hypothesised as the major target;[40] however, this was recently contradicted by further experiments on murine models.[41]

Luspatercept (ACE-536) is an activin Type IIA ligand trap, binding to several members of the TGF-β superfamily. It has recently been approved by the U.S. Food and Drug Administration (FDA) and by the European Medicines Agency (EMA)[42] for the treatment of anaemia in TDT and EPO-refractory myelodysplastic syndrome with ring sideroblasts. Results from a Phase II trial[43] led to the initiation of the randomised, Phase III BELIEVE clinical trial[44] of luspatercept in 336 adult patients with TDT in 15 countries. The percentage of patients who had a minimum reduction of 33% of transfusion burden was higher in the luspatercept arm than the placebo arm for fixed predefined time periods (from baseline to Weeks 13–24: 21.4% versus 4.5%; from baseline to Weeks 37–48: 19.6% versus 3.6%, respectively) and during any 12-week period (70.5% versus 29.5%, respectively). Subgroup analysis revealed that the magnitude and rapidity of response might be lower in patients with a β^0/β^0 genotype than in patients with a non-β^0/β^0 genotype. Adverse events were mainly Grade 1 and 2 and consisted of bone, back, and musculoskeletal pain, headache, myalgia, arthralgia, and injection site pain. However, in this randomised trial, eight thromboembolic events (deep vein thrombosis, ischaemic stroke, superficial thrombophlebitis, pulmonary embolism) were reported, all in patients who had previously undergone splenectomy.

Given the central role of the JAK2/STAT5-signalling pathway in EPO/EPO receptor interaction on erythroblasts,[45] JAK2 inhibition was tested as a potential mechanism for reversing ineffective erythropoiesis. Despite initial promising results,[46] when ruxolitinib was tested in a Phase IIa study for patients with TDT with spleen enlargement, no significant Hb increase from baseline was observed nor significant changes in total body iron concentration.[47]

Gene Therapy: Gene Insertion Approaches

While HCT has long-been considered the only curative treatment for thalassaemias, its applicability is hampered by the availability of a full-matched, HLA-identical donor, by the risk of immunological complications, and by the need for long-term immunosuppression. The goal of current gene therapy is to provide a curative option for patients lacking HLA-identical siblings by inducing the production of the β-globin or γ-globin, thus improving the α/non-α globin ratio, decreasing the deposition of insoluble α-hemichromes, and correcting ineffective erythropoiesis. This can be achieved through two different major platforms: gene insertion and gene editing.[48]

The first approved gene therapy product approved in Europe for the treatment of patients with TDT aged ≥12 years with a non-β^0/β^0 genotype, candidates for HCT but lacking an HLA-identical sibling, is LentiGlobin BB305,[49] approved in 2019, and belongs to the first category; this consists of inserting a lentiviral vector containing the β-globin-producing genes together with their regulatory machinery (promoter, enhancer, and part of the locus control region) into previously collected autologous haematopoietic peripheral blood stem cells (PBSC) and later infusing these genetically modified PBSCs back into the patient after proper myeloablation to facilitate engraftment.[50] The β-globin-producing sequences are placed under the control of an erythroid promoter, so that they can only be transcribed in erythroid precursors. However, this process remains fairly

uncontrolled and, despite the optimisation of the more recent lentiviral vectors, occurs 'semi-randomly', potentially retaining a risk of clonal proliferation stimulation.[52] For this reason, the FDA and EMA require a total follow-up of 15 years for all patients treated with gene therapies.

LentiGlobin BB305 was tested in two Phase I/II trials on a total of 22 patients aged 12–35 years with TDT of any genotype.[52] The conditioning regimen consisted of myeloablative doses of busulfan modulated by pharmacokinetic (PK) analysis. All patients attained engraftment and 10% developed veno-occlusive disease and required defibrotide treatment. The vector copy number of infused products ranged from 0.3 to 1.5 in the first trial and from 0.8 to 2.1 in the second trial. The gene-insertion-derived HbA, separately identified by liquid chromatography due to an amino-acid substitution (HbA^{T87Q}), was produced at an average of 6 g/dL in non-$\beta^0\beta^0$ genotypes, granting transfusion independence in all but one patient. Subsequent efforts have focused on improving the transduction process, elevating the vector copy number of the final product to a median of three copies per double-stranded DNA. The results of the Phase III Northstar-2 and Northstar-3 trials show a stable Hb ≥11 g/dL in 91% of patients with non-$\beta^0\beta^0$ genotype,[53] and 3 out of 4 $\beta^0\beta^0$ patients followed-up for ≥6 months having stopped transfusions.[54] The commercialisation of LentiGlobin for TDT has recently been suspended after two myeloid neoplasms were diagnosed in patients with treated sickle cell disease during follow-up.[55] These events will need to be clarified before proceeding with a large clinical application.

In Italy, nine patients were treated with the GLOBE lentiviral vector-transduced autologous haematopoietic PBSCs, with intra-bone administration to avoid trapping into filter organs and allow for better and earlier haematopoietic recovery.[56] The most significant gene therapy clinical trials conducted so far in TDT are listed in Table 2.[52-57]

Although gene therapy overcomes the risk of graft-versus-host disease and the need for a suitable donor, there are several challenges still to be faced. 1) Busulfan-based myeloablative conditioning is not devoid of toxicity and some attempts have been made to minimise it, such as dose-tailoring based on PK[54] or the use of the less-toxic thiotepa and treosulfan.[56] 2) Long-term follow up is still not available and the number of treated patients so far is not enough to have a complete safety profile. 3) A large number (≥10–15x10^6 CD34+/kg) of stem cells is required to account for stem cell losses during manufacturing, demanding for upfront plerixafor.[58] 4) Unlike stem cell transplantation, where the β-globin defect correction occurs in a pan-cellular fashion (e.g., in every donor-derived stem cell), the number of gene insertions in PBSC can vary depending on the efficiency of manufacturing processes, leading to a heterocellular correction and strongly demanding for an adequate characterisation of the product prior to infusion, at least in terms of viability, purity, and efficiency of the transduction process.[48] 5) In order to be potentially manufactured on a large scale, costs and quality of life should be superimposable compared to alternative-donor HCT, and a socioeconomic advantage over the costs of life-long transfusions and chelation should be demonstrated.

FUTURE TREATMENTS

Gene Therapy: Gene Editing Approaches

The gene editing approach exploits the possibility to precisely cut human DNA at specific locations by engineered nucleases, such as zinc-finger nucleases and CRISPR/Cas9.[60] By doing so, they can either act on specific erythroid enhancer regions regulating the switch from the γ-globin genes to the β-globin genes, or recreate the mutations seen in hereditary persistence of fetal Hb, thus incrementing the production of fetal Hb. This method retains the advantage of a higher precision and efficiency in DNA edits and of more affordable costs.[49]

Recently, the results of the first patient treated with a CRISPR/Cas9 gene-editing product, targeting the enhancer of the *BCL11A* gene on chromosome 2, were presented (CTX001 product): the patient (β^0/IVS-1-110 genotype) was transfusion-independent at 12-months follow-up and 99% of erythrocytes expressed high levels of fetal Hb.[60]

Table 2: Gene insertion approaches in clinical trials.

Study; Sponsor	Vector	Number of patients	Genotype	Conditioning	Graft source; administration route	Results
HGB-204 and HGB-205, Thompson et al.,[53] 2018; Bluebird	BB305 T87Q encoding human β-globin LV vector (former HVP569) with removal of insulators	22	TDT all genotypes	PK-guided busulfan	mPBSC; intravenous	12/13 non-$\beta^0\beta^0$ patients became TI 3/9 $\beta^0\beta^0$ patients became TI
HGB-207 Northstar-2, Thompson et al.,[54] 2019; Bluebird	As above	20	TDT non- $\beta^0\beta^0$ genotype	PK-guided busulfan	mPBSC; intravenous	4/5 evaluable patients became TI
HGB-212 Northstar-3, Lal et al.,[55] 2019; Bluebird	As above	11	TDT either β^0 or β^+ IVS-I-110 mutations on both *HBB* alleles	PK-guided busulfan	mPBSC; intravenous	3/4 evaluable patients became TI
TIGET-BTHAL, Marktel et al.,[57] 2019; Telethon Foundation	GLOBE lentiviral vector	9	TDT either $\beta^0\beta^0$ or severe β^+ genotypes	RTC treosulfan + thiotepa	mPBSC; intrabone	3 adults reduced transfusion requirements 3/4 evaluable children became TI
NCT 01639690, Maggio et al.,[58] 2020; Memorial Sloan Kettering	TNS9.3.55.A1	Target=10	β-thalassaemia major, transfusion dependent	Busulfan 8–14 mg/kg	mPBSC; intravenous	Estimated completion date: July 2021; 2/3 evaluable patients reduced transfusion requirements

mPBSC: Mobilised peripheral blood stem cells; PK: pharmacokinetics; RTC: reduced toxicity conditioning; TI: transfusion independent; TDT: transfusion-dependent thalassaemia.

More attempts are ongoing with CRISPR/Cas12 products performing edits on the *BCL11A* binding site on the *HBB* gene; this process demands extreme precision in order to prevent disruption of endogenous globin production.[61] The main limitation lies in the risk to create unintended edits in the genome ('off-target effects'), although this is not necessarily of clinical significance;[62] additionally, chromosomal rearrangements or instability can occur and require serial monitoring.[63]

Iron Metabolism Modifying Agents (Minihepcidines, Ferroportin Inhibitors)

The hepcidin/ferroportin axis is a major regulator of erythropoiesis; ineffective erythropoiesis with low or inappropriately normal hepcidin levels and subsequent iron overload are hallmarks of the so-called 'iron-loading anaemias', with NTDT as a prototype,[64] thus the possibility to therapeutically target this axis has recently gained some interest.

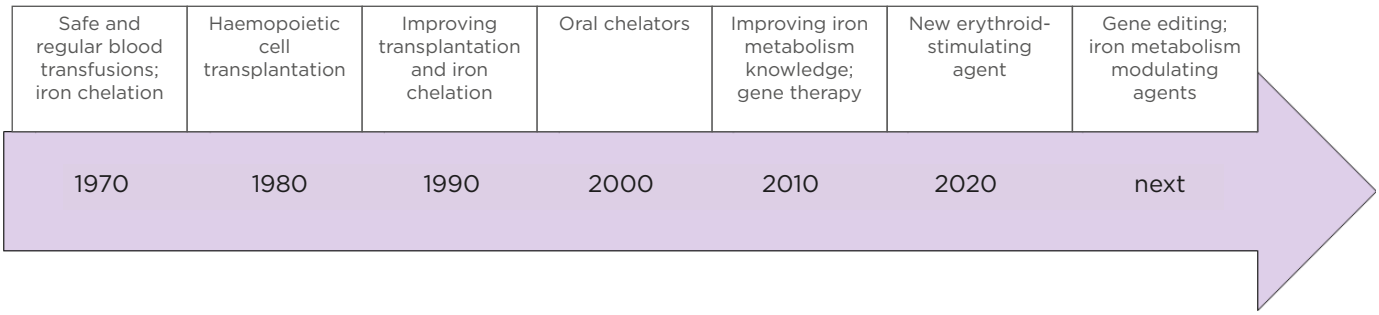

Figure 1: Milestones of therapeutic advances in β-thalassaemia, revealing continuous improvement during recent decades.

Studies on β-thalassaemia in mouse models demonstrated that transgenic overexpression of hepcidin or genetic disruption of hepcidin regulators can result in the prevention of iron overload and enhance haemopoiesis.[65] Biosynthesis of full-length hepcidins is inefficient and they are rapidly cleared by the kidneys; however, these limitations were somehow overcome by the development of minihepcidins (MH): short, engineered peptides with an increased half-life and potency, able to mimic the iron-restrictive effect of endogenous hepcidin.[66] In young $Hbb^{th3/+}$ mice, serving as models for NTDT, MH ameliorated anaemia, ineffective erythropoiesis, splenomegaly, and iron overload. In older mice, the administration of MH together with deferiprone did not modify its beneficial effect on iron overload.[67] In TDT mice models, MH in combination with chronic red blood cell transfusions further improved ineffective erythropoiesis, splenomegaly, and iron overload. Based on these results, multiple trials were started to assess efficacy of MH in the clinical setting. In a Phase II study, LJPC-401 was tested for the treatment of myocardial iron overload in patients with TDT but the trial was prematurely terminated because of absence of efficacy.[68]

Another approach to modulate iron metabolism is through ferroportin inhibitors. Among these, VIT-2763 is a small, oral compound that competes with hepcidin for ferroportin binding. In the $Hbb^{th3/+}$ mice, it ameliorated ineffective erythropoiesis and the dysregulated iron homeostasis; it also corrected the proportion of myeloid precursors in $Hbb^{th3/+}$ mice spleens.[69] A Phase I, double-blind, dose-escalating study was performed in order to assess for safety, tolerability, PK, and pharmacodynamic properties of VIT-2763 in healthy volunteers: no serious events led to drug discontinuation and most of the adverse events in the single and multiple escalating dose cohorts were drug-unrelated; a temporary decrease in mean serum iron and mean transferrin saturation were observed.[70] A Phase II, randomised, double-blind trial assessing efficacy, safety, and tolerability of VIT-2763 is currently recruiting in multiple sites.[71]

CONCLUSION

The last 50 years have witnessed dramatic improvements in thalassaemia understanding and patient care. These improvements have built a series of previously unimaginable therapeutic opportunities for patients with thalassaemia, with many more on the way. All of this was made possible by a synergy between the various fields of biological and clinical research, which have mutually reinforced one another to lead to shared success. Figure 1 reports the milestones of therapeutic progress in β-thalassaemia.

Having access to many therapeutic opportunities is undoubtedly beneficial for patients, yet it can also lead to problems when choosing treatment. As opportunities have grown, the cost of optimal therapies has increased dramatically, and so has the demand for a better selection of the appropriate sequence of treatments in terms of cost/benefit ratio. When compared to HCT (the only other available curative option), gene therapy results

in, on average, an additional 300,000–400,000 EUR/patient, justified by the high costs of the viral vector and preparation procedures. On the other hand, as competition between different suppliers grows and follow-up monitoring becomes less stringent, the whole procedure should become more affordable;[72] nonetheless, requirements in terms of professional skills, quality efficacy, and regulatory compliance still make it an unattractive approach in low-income countries. Traditional treatments, on the other hand, are not devoid of costs, estimated around 30,000 EUR/year/patient for TDT in Italy,[73] making HCT at younger ages, when feasible, probably the most appropriate choice in the circumstance, even in terms of resource application. In conclusion, in order for the points discussed in this article to become common practice, an effort must be made to progress, consistent with resource availability and still crucially impacting the real opportunities for benefiting from these advances in the real world.

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Recurrent Episodes of Angioedema as Presenting Feature of *JAK2*-Positive Myeloproliferative Disorder Consistent with Polycythaemia Vera

Authors: Laith Al-Azrai,[1] *Ala'a Abdullah Bani Mustafa,[2,3] Adi Yousef al-Wahadneh[2]

1. Department of Internal Medicine, Queen Alia Military Hospital, Amman, Jordan
2. Department of Internal Medicine, King Hussein Medical Hospital, Amman, Jordan
3. Department of Internal Medicine, Ministry of Health, Dr Jameel al Totanji Hospital, Amman, Jordan

*Correspondence to alaa.banimustafa@yahoo.com

Disclosure: The authors have declared no conflicts of interest.

Acknowledgements: This study was initiated and supported by the Royal Medical Services, Amman, Jordan. The authors would like to thank the institutional review board for their tremendous support. They also wish to give special thanks to Majed al Habahbeh and Gheith al Hassan for their comments that greatly improved the manuscript. Special thanks to the laboratory team in Royal Medical Services and al Khaldi Hospital.

Received: 15.12.20

Accepted: 05.03.21

Keywords: Angioedema, *JAK2* mutation, myeloproliferative disorder, polycythaemia vera (PV).

Citation: EMJ Hematol. 2021;9[1]:105-109.

Abstract

Polycythaemia vera (PV) is one of the chronic myeloproliferative neoplasms, which are collectively characterised by clonal proliferation of myeloid cells with variable morphologic maturity and haematopoietic efficiency. PV is distinguished clinically from other myeloproliferative neoplasms by the presence of an elevated red blood cell mass because of uncontrolled red blood cell production. This is accompanied by increased white blood cells and platelet production, which is because of abnormal clone of haematopoietic stem cells with increased sensitivity to the different growth factors for maturation. PV can present with variable symptoms because of impaired oxygen delivery caused by slugging of blood, such as headaches, dizziness, vertigo, tinnitus, visual disturbances, and angina pectoris.

Some patients present with bleeding complications (1%); another 1% of patients present with thrombotic complications. It is uncommon for patients with myeloproliferative disorders to present with features of angioedema. There are many reported cases in the literature that describe the relationship between the occurrence of angioedema and lymphoproliferative diseases; however, there are no reported cases describing instances of myeloproliferative neoplasm with angioedema.

In this article, the authors have studied a case of a 53-year-old male who presented with recurrent episodes of features that are suggestive of angioedema. He was diagnosed with *JAK2*-positive myeloproliferative disorder consistent with PV; this is the first reported case in Jordan.

INTRODUCTION

Polycythaemia vera (PV) is a condition characterised by an increasing number of the red blood cells in the blood.[1] It is usually caused by a change in the *JAK2* gene; affected bone marrow cells can also develop into other cells found in the blood, which means that patients with PV may also have abnormally high numbers of both platelets and white bloods cells.[2] Conditions where the body makes too many of these cells are known as myeloproliferative neoplasms.[1] The type of myeloproliferative neoplasm is based on whether too many red blood cells, white blood cells, or platelets are being made. Sometimes the body will make too many of more than one type of blood cell, but usually one type of blood cell is affected more than the others.[3]

Extra cells in the bloodstream cause the blood to be thicker than normal, which increases the risk for blood clots that can block blood flow in arteries and veins.[3] There are several types of myeloproliferative disorders. The most common are PV, essential thrombocythaemia, primary myelofibrosis, and chronic myelogenous leukaemia.[4]

Annual incidence of PV is estimated at approximately 1/36,000–1/100,000 and prevalence at 1/3,300.[5] PV is an acquired disease during a person's life time; rarely it is inherited in an autosomal dominant pattern.[6] PV becomes more common as an individual ages and typically presents for the first time around 60 years old. It is more frequent in males than in females and is associated with mutations in *JAK2* and *TET2* genes.[7]

The *JAK2* gene provides cell instruction for making JAK2 protein. The JAK2 protein is important for controlling blood cell production in bone marrow from haematopoietic stem cells; it promotes cell division and plays a major role for transmitting signals from outside the cell to the cell's nucleus through a signalling pathway called JAK–STAT pathway.[8]

JAK2 mutation is a change of valine to phenylalanine at 617 position (*JAK2* V617F). This mutation causes haematopietic cells in the bone marrow to become more sensitive to growth factors such as erythropoietin and thrombopoietin, which leads to over-production of red blood cells, white blood cells, or platelets. This mutation is present in the majority of patients with myeloproliferative neoplasm, nearly 100% of patients with PV, and in approximately 50% of essential thrombocytosis and primary myelofibrosis.[9]

Because patients with PRV have thicker blood, this can lead to serious health problems such as heart attack or stroke.[5] Impaired O_2 delivery due to slugging of blood may lead to variable symptoms such as headache, dizziness, vertigo, tinnitus, visual disturbances, angina pectoris, or intermittent claudication.[10] In patients with PV, those with a haematocrit target of <45% had a significantly lower rate of major thrombosis than those with a haematocrit target of 45–50%.[11]

It is uncommon for patients with myeloproliferative disorders, including PV, to present with features of acquired angioedema. Acquired angioedema is due to the acquired deficiency of C1-inhibitor, which was first described in a patient with high-grade lymphoma and is frequently associated with lymphoproliferative diseases.[12]

C1-inhibitor is a serine protease inhibitor, primarily synthesised by hepatocytes. Its synthesis is upregulated by interferon-γ, IL-6, IL-1, and androgens. C1-inhibitor inhibits the activation of *C1R*, *C1S*, activated Hageman factor (x11a), and kallikrein. Kallikreins are proteases that cleave kininogen and release bradykinin. Bradykinin exhibits its effect through activation of bradykinin B2 receptor in the membranes of endothelial and smooth muscle cells, and plays a major role in tissue permeability and vascular dilatation. Elevated blood bradykinin levels are found during clinical flares in patients with angioedema.

There are two types of acquired angioedema: Type I and II. In acquired angioedema Type I, the disorder usually associated with lymphoproliferative malignancies, antibodies or immune complexes are produced that destroy C1-inhibitor function. The most common associated malignancy with this type is B-cell lymphoma. In acquired angioedema Type II, a normal C1-inhibitor molecule is synthesised in adequate amounts but, because of unknown events, autoantibodies to the C1-inhibitor molecule bind to the reactive centre of C1-inhibitor, alter its structure, and impair its regulatory capacity.[13] It is unknown which

one of these myeloproliferative disorder mechanisms cause acquired angioedema.

There is no consensus as to the optimal therapy for the disorder,[14] but treatment is aimed at reducing the chance of the patient developing symptoms and complications. The main treatments are venesection and medication to help slow the production of red blood cells.[15] Myelosuppressive drugs can reduce the rate of thrombosis in those patients, but there is concern that their use raises the risk of transformation into acute leukaemia; the drug of choice is hydroxyurea because of its efficacy in preventing thrombosis and low leukaemogenicity.[16]

Many articles have described the relationship between the occurrence of angioedema and lymphoproliferative diseases, but not myeloproliferative ones. In this article, the authors studied a rare case of a 53-year-old male who presented with recurrent episodes of features suggestive of angioedema, who was diagnosed with PV.

CASE REPORT

A 53-year-old male patient, who was a non-smoker with no known prior medical illnesses, presented to the emergency room with recurrent episodes of swelling of his lips and face. The swelling occurred spontaneously, was not itchy, and disappeared without intervention after a few hours but reoccurred every 5–6 days. His symptoms were associated with mild, diffuse abdominal pain and nausea.

The swelling was not preceded by any drug ingestion or exposure to any irritant, such as plants or dust, and was not accompanied by skin rash. He denied any history of insect bites or previous similar symptoms.

His medication history was reviewed to exclude angiotensin-converting enzyme inhibitor-induced angioedema. He described the feeling of itch after hot baths. He had no shortness of breath, no sore throat, no fever, and no dizziness, and other elements of review of systems were unremarkable.

His physical examination was normal except for the presence of lip and periorbital swelling. His vital signs were stable and his O_2 saturation readings were always >94%. Chest, cardiovascular system, abdomen, and lower limb examinations were unremarkable.

A routine complete blood count during his second month of symptoms was undertaken: white blood cells 10.94 million cells/μL; red blood cells 7.97 million cells/μL; haemoglobin 18.8 gm/dL; haematocrit 60%; mean corpuscular volume 75 fL; platelets 709x10^9/L; neutrophils 70%; lymphocytes 17.2%; monocytes 9.5%; eosinophils 2.7%; basophils 0.5%; erythropoietin level 3 μ/L; and vitamin B12 154 ng/mL.

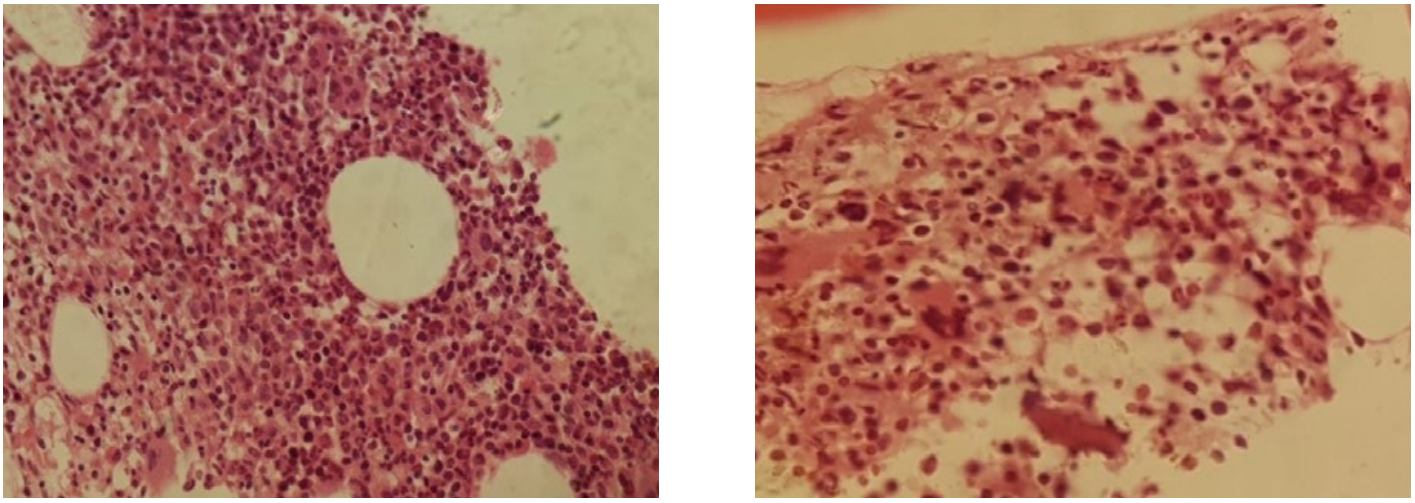

Figure 1: Bone marrow aspiration, showing hypercellular bone marrow with no fibrosis.

The erythrocyte sedimentation rate was 2, and antinuclear antibodies were negative. Regarding complement components, C2, C4, thyroid-stimulating hormone, thyroxine, and ferritin were unremarkable. Blood film showed hypochromic, microcytic erythrocytosis with thrombocytosis and neutrophilia.

Findings of bone marrow aspiration were suggestive of myeloproliferative neoplasm with features of PV, complicated by iron deficiency (Figure 1). Microscopic examination of the bone marrow revealed hypercellular bone marrow for age, with an estimated cellularity of 90%. Erythroid precursors were increased, and granulocytic precursors were increased with normal maturation and differentiation. Megakaryocytes were increased, forming clusters with pleomorphic morphology. Reticulin stain showed no marrow fibrosis. Masson's trichrome stain showed no collagenous fibrosis.

Ultrasound of the abdomen revealed a liver measuring 18 cm that was slightly increased in echogenicity. The spleen appeared homogenous, measuring 14 cm.

The patient was positive for *JAK2* V617F mutation and negative for *BCR-ABL1*. His C1 esterase inhibitor level was 0.437 g/L (normal level: 0.15–0.35); however, blood sampling for this test was taken two weeks after commencing hydroxyurea, and not during an acute attack of angioedema, which may have affected the results.

DISCUSSION

The myeloproliferative disorders are clonal disorders of multipotent haematopoietic progenitors and include PV, essential thrombocythaemia, primary myelofibrosis, and chronic myelogenous leukaemia. Most patients with PV, essential thrombocythaemia, and primary myelofibrosis acquire a single point-mutation in the cytoplasmic tyrosine kinase *JAK2 (JAK2* V617F).[17] There are several criteria to diagnose PV and those criteria depend upon the presence or absence of *JAK2* mutation. A previously published study explained the criteria of PV diagnosis:[18]

- Haemoglobin >16.5 g/dL in males or >16 in females, or haematocrit >49% in males and >48% in females.
- Bone marrow biopsy showing hypercellularity for age.
- Presence of *JAK2* V617F mutation.

It was unexpected for a patient with PV to exhibit features of angioedema. Acquired angioedema is characterised by an acquired deficiency of C1-inhibitor, hyperactivation of the classical pathway of human complement, and angioedema symptoms mediated by bradykinin released by inappropriate activation of the contact–kinin system.[19] C1-inhibitor acquired angioedema typically presents with recurrent attacks that most commonly involve the tongue, uvula, upper airways, and face, although other areas of the body can be affected.[20]

There is no cure for PV; treatment focuses on reducing the risk of complications.

Treatment to lower red blood cell levels involves phlebotomy, medications such as hydroxyurea and interferon-α, and radiation treatment, which can help suppress overactive bone marrow cells but raises the risk of leukaemia. Aspirin can relieve bone pain and burning feelings in the hands or feet and reduce the risk of blood clots.[21]

The discussed patient met all of these criteria for diagnosis of PV. He presented with signs and symptoms of angioedema; although his C1 esterase levels were high, as mentioned the sample was taken after initiation of hydroxyurea and the patient was not experiencing an acute attack, which may have affected the result.

The authors reviewed his medication history to exclude drug-induced angioedema. He denied any history of insect bite or exposure to new food or any allergens. His C4 and C2 levels were normal and there was no family history of angioedema. He responded temporarily to antihistamines and steroids, but once he was commenced on hydroxyurea he did not develop any further episode of angioedema, although his haematocrit remains high, meaning that hydroxyurea may affect the presence of autoantibodies against C1-inhibitor.

The patient was encouraged to exercise regularly, which can improve blood flow and decrease risk of blood clots. He was also advised to avoid low-oxygen environments and extreme temperature.

Underlying lymphoproliferative malignancies are common in patients who are seen initially with

late-onset angioedema.[22] There are no instances of myeloproliferative neoplasm with angioedema currently reported in the literature and this is the first reported case in Jordan to describe the onset of angioedema as the presenting feature of myeloproliferative disorder; however, further investigations are needed for similar cases. In addition, this highlights the importance of holding high clinical suspicion for neoplasm in adults presenting with angioedema. The authors thank the patient for granting permission to publish this information.

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Glanzmann Thrombasthenia: A Case Report of a Rare Inherited Coagulation Disorder Presenting with Traumatic Head Injury

Authors: Vishal Chakati,[1] Durga Prasad Bukka,[1] Srinivas Rao Erigaisi,[2] *Shyam Sunder Anchuri[1]

1. Department of Pharmacy Practice, Balaji Institute of Pharmaceutical Sciences, Telangana, India
2. Srinivasa Pinnacle Neuro & Multispeciality Hospital, Hanmakonda, India

*Correspondence to shyamar9@gmail.com

Disclosure: The authors have declared no conflicts of interest.

Received: 17.01.21

Accepted: 16.04.21

Keywords: Consanguineous, glycoprotein, platelets, thrombasthenia, traumatic head injury.

Citation: EMJ Hematol. 2021;9[1]:110-113.

Abstract

This case study deals with a 32-year-old Indian male patient who presented with a traumatic head injury in the hospital, experienced uncontrolled bleeding after conducting surgery, and was eventually diagnosed with Glanzmann thrombasthenia. Glanzmann thrombasthenia is a rare hereditary blood clotting disorder characterised by a lack of platelet aggregation due to the absence of platelet glycoprotein IIb/IIIa. This occurrence is generally triggered by consanguineous marriages and is apparent in approximately one in one million people. Education and raising awareness about consanguinity in communities may help to reduce challenging, unusual genetic diseases.

INTRODUCTION

Eduard Glanzmann first reported Glanzmann thrombasthenia (GT) in 1918 after he identified a functional abnormality of platelets with defective clot retraction. Glanzmann thrombasthenia is a rare autosomal recessive disorder with normal or sub-normal platelet count, prolonged bleeding time, and deficiency or absence of platelet aggregation.[1,2] It is a rare genetic platelet disorder in which the platelet glycoprotein IIb/IIIa (GPIIb/IIIa) complex is affected, with an occurrence of one in one million.[3] It is commonly seen in populations with an autosomal recessive pattern of inheritance with increased consanguinity. An acquired form of GT in which autoantibodies to the glycoprotein complex interfere with normal functioning has also been reported.[4]

Integrin $\alpha_{IIb}\beta_3$, formerly known as GPIIb/IIIa, is a platelet receptor for fibrinogen. It shifts to its active configuration to allow for fibrinogen binding when platelets are activated. As platelets bind the fibrinogen, they accumulate and provide primary haemostasis. Bleeding can be spontaneous or occur with an injury without functioning fibrinogen receptors or without enough of them.[5,6] Platelets in GT are not as effective in producing thrombin, an integral part of converting fibrinogen to fibrin.[7] When cross-linked fibrin stabilises the platelet plug, secondary

haemostasis occurs and is thus also affected by GT.[8]

There are three groups of GTs in patients: Type I, Type II, and variations. Patients with Type I have <5% of GPIIb/IIIa; patients with Type II have 5–20% of the average amount of GPIIb/IIIa; and patients with variant types have one-half of the average quantities of GPIIb/IIIa. Type I is the most prevalent, but there is little connection between the seriousness of the disease and the subtypes. Purpura, epistaxis, gingival haemorrhage, and menorrhagia are the recurring features seen in GT, as well as excessive bleeding following dental extraction and surgery.[6]

CASE DESCRIPTION

A 32-year-old Indian male patient with loss of consciousness presented to the emergency department shortly after a serious traumatic head injury. He had undergone one episode of seizure at the time of the accident. There were no other comorbidities, he was a non-smoker, and had an occasional alcohol use disorder. He had no immediate family support system. Due to the head injury, the patient underwent radiological tests including a CT brain scan that revealed a right temporoparietal intracranial haematoma. The neurosurgeon immediately performed decompressive craniotomy surgery. The operation profile revealed haemoglobin 12.7 g/dL (normal range: 13–18 g/dL); blood group O; positive Rhesus typing; bleeding time of 2 minutes and 10 seconds (normal range: 1–3 minutes); clotting time of 3 minutes and 40 seconds (normal range: 3–7 minutes); random blood glucose of 162 mg/dL (normal range: 60–140 mg/dL); blood urea 29.0 mg/dL (normal ranges: 10–40 mg/dL); serum creatinine of 0.8 mg/dL (normal range: 0.6–1.5 mg/dL); negative hepatitis B surface antigen; negative for HIV-1 and -2; and negative for hepatitis C virus 1 and 2. During the surgery, there was uncontrolled bleeding at the surgical site despite all measures being taken to control the bleeding. Two pints of blood were immediately transfused. After controlling the bleeding, the haematoma was removed, and the surgical site was closed in layers.

Six units of fresh frozen plasma and two bottles of blood were post-operatively transfused, and the patient was examined for further haematological tests such as activated partial thromboplastin time (PTT; 35.7 sec); mean normal PTT (32.2 sec); prothrombin time (PT; 17.4 sec); mean normal PT (13.1 sec); and international normalised ratio (1.57). Re-examination of PT with international normalised ratio revealed 16.0 sec increase and activated PTT of 29.6. Other laboratory tests were performed on serum electrolytes: sodium (139 mmol/L); potassium (4.1 mmol/L); and chloride (99 mmol/L). A complete blood picture showed total white blood cell count of $12x10^9$/L, a differential count of neutrophils (92%), eosinophils (1%), lymphocytes (55%), monocytes (2%), basophils (0%), haemoglobin (12.7 g/dL), total red blood cell count (4.6 million/mm^3), and platelet count ($194x10^3$ /mm^3).

After the surgery, repeat CT brain scan (plain) showed right-sided temporoparietal and frontal contusions with moderate mass effect, for which emergency re-exploration surgery was performed. During the emergency re-exploration, the surgeons evacuated the temporal intracranial haematoma but the frontal haematoma was deferred. At the time of surgery, there was another bout of uncontrolled bleeding that lasted for 1 hour despite compression with AbGel®©™ surgical cottonoids (Shri Gopal Krishna Labs Pvt. Ltd., Mumbai, India).

The emergency re-exploration surgery and CT cerebral angiogram revealed decreased haematoma in the right temporoparietal region with air foci within the stable size of the right frontal haematoma; stable intraventricular haemorrhage and tentorial haemorrhage; persistent mass effect over the right lateral ventricle with mild midline shift to the left (5 mm); and no evidence of aneurysm or any focal stenosis.

For the case of uncontrolled bleeding during surgery, the haematologist carried out a platelet aggregometry test (Table 1) and the results revealed a GT diagnosis. Upon diagnosis, the patient's caregiver was thoroughly questioned and revealed that the patient was born to consanguineous parents. A plain CT brain scan

revealed the right frontal, temporal, parietal decompressive craniotomy, and the right frontal contusions slowly resolved during the hospital stay. In post-operative care, the patient was treated with supportive care, intravenous fluids, antibiotics, analgesics, anticonvulsants, anti-oedema measures, proton pump inhibitors, and anti-emetics. After haemodynamic stability, the patient was discharged with a good clinical response.

DISCUSSION

GT is an inherited platelet function disorder and is extremely rare except in populations where consanguineous marriages are common such as in Iranian, Southern Indian, and Iraqi Jewish populations.[9,10] Toogeh et al.[11] conducted a retrospective descriptive study of 382 patients and concluded that most cases of GT were consanguineously born. Nelson et al.[12] identified 15 unrelated patients diagnosed with GT, 11 of whom were born to consanguineous parents and six with a family history of bleeding. The authors concluded that their results confirmed the genetic diversity of mutations and polymorphisms in α_{IIb} and β_3 genes in patients with GT in Southern India and provided insight into the structure and function of relationships in these genes, but they did not identify any clear genotype or phenotype correlations. In this current study, the patient was born to consanguineous parents.

Early reports addressed the clinical heterogeneity of this bleeding syndrome: some patients had minor bruising, while others had regular, serious, and possibly fatal bleeding. Haemorrhagic symptoms occurred only in patients who were homozygous for GT-causing mutations; heterozygous diseases are often asymptomatic, although they have only a semi-normal platelet $\alpha_{IIb}\beta_3$ concentration.[13] Zheng et al.[14] explored the mechanisms underlying thrombocytopenia and the bleeding phenotype in a patient with acquired GT, concluding that platelet desialylation was mediated by anti-Fc-γ receptor IIa, independent of platelet activation, in a patient with acquired GT.

In most cases, there were rapid clinical signs of bleeding after birth, even though GT is rarely diagnosed later in life. Epistaxis is a common cause of serious bleeding and is usually more severe in childhood.[15] Gopalakrishnan et al.[16] reported a case on medical and surgical management of an 11-year-old female diagnosed with GT who had undergone maxillary cyst enucleation. They concluded patients diagnosed with GT show signs of bleeding very early in life.

Duncan et al.[17] conducted research on GT to identify the burden of disease for patients and caregivers through a better understanding of the management and psychosocial impact of this disorder, concluding that most patients with GT are diagnosed early, with >50% of participants diagnosed with GT within 1 year.

Much of the literature has concluded that GT is diagnosed early, in contrast to this study in which the patient had GT newly diagnosed during surgery at the age of 32.

Cherian et al.[18] detailed a 28-year-old male with GT who received a late diagnosis. Swathi et al.[19] identified an 18-year-old female who had a recent diagnosis of GT but had a history of prolonged bleeding after mild trauma, a

Table 1: Platelet aggregometry test.

Test name	Result (%)	Biological reference interval (%)
Adenosine diphosphate	0	61–82
Collagen	0	62–82
Ristocetin	83	66–92
Epinephrine	0	52–82

propensity to bleed, including purpura in areas of easy bruising, gum bleeding, and prolonged bleeding time after abrasions and insect stings.

GT, like many other bleeding disorders, has a multi-tiered treatment structure. Initial care for minor bleeding episodes may include local pressure, cauterisation, sutures, or ice therapy.[20] Platelet transfusion is routine for GT as surgical prophylaxis and treatment for moderate to serious bleeding. Many patients benefit from preventative care and symptomatic treatment. Curative treatment with haematopoietic stem cell transplant has been effective in a limited number of patients with GT who have an extremely poor quality of life. Family planning discussions, which include the possibility of childbirth and the children who will be affected, are also important for some patients.[7,8]

CONCLUSION

This case report highlights a case of newly diagnosed GT at 32 years of age, during surgery. GT is a rare hereditary bleeding disorder caused mainly by consanguineous marriages. Education and creating awareness of these marriages is a good preventive method as they are at higher risk of rare genetic disorders.

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