EMJ HEMATOLOGY

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+ EHA25 VIRTUAL CONGRESS 2020

Reviewed

+ INTERVIEWS

Five EHA Committee Chairs and Members discuss their positions and current challenges in the field of haematology.

+ ABSTRACT REVIEWS

Enthralling reviews of abstracts presented at EHA25 Virtual with topics including Fanconi anaemia, Hodgkin lymphoma, and chronic myeloid leukaemia.

+ EDITOR'S PICK

Pregnancy-Related Thromboembolism in Sickle Cell Disease

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"Haematologists and other clinicians of the speciality will appreciate the variety of content within this eJournal, as we have ensured that field-leading topics in the therapeutic area have been covered"

Spencer Gore, CEO

Editorial Board

VIEW IN FULL ←

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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EMJ Hematology 8.1

Welcome

Dear Readers,

As we pass into the second half of this unprecedented year for the medical community, we offer some normality in the form of our annual publication, *EMJ Hematology*. Inside you will find all your usual favourites, such as peer-reviewed articles, an independent review of the 25th European Hematology Association (EHA) Annual Congress (EHA25 Virtual), interviews with experts in the field, and abstract summaries from the EHA congress to bring you up to date with the latest in haematology.

Rather than attending the EHA Annual Congress in Frankfurt, Germany, we instead had the pleasure of attending the meeting in the comfort of our homes as we embraced this new era of virtual platforms, meaning that so many key congresses this year can still continue with their goals of research dissemination. Included in our review of EHA25 Virtual, we have an in-house feature based on a congress session, titled 'Coagulopathy and Hyperinflammation in COVID-19', as well as summaries of the congress' late-breaking abstracts, which cover the subject areas of radiotherapy omission and how it impacts survival in Hodgkin lymphoma and the hopeful treatment for steroid-refractory acute graft-versus-host disease.

Also presented within *EMJ Hematology* are exclusive congress committee interviews; our editorial team had the pleasure of interviewing Prof Margarita Guevova, EHA Chair of European Board for Accreditation in Hematology; Prof Antonio Almeida, EHA Chair of the Curriculum Committee; and Dr Noémi Roy, EHA Guidelines Committee Chair.

Haematologists and other clinicians of the speciality will appreciate the variety of content within this eJournal, as we have ensured that field-leading topics in the therapeutic area have been covered, maintaining our integrity in providing clinically relevant research to healthcare professionals. All that remains is for me to thank the Editorial Board, authors, interviewees, and you, the readers, for your loyalty, as we continue to be the go-to place for healthcare professionals.

Spencer Gore

Chief Executive Officer, EMG-Health

Foreword

Dear Readers,

For the last 8 years *EMJ Hematology* has provided the most up-and-coming, exciting developments in the field of haematology. Despite the SARS-CoV-2 pandemic, we stay faithful to our goals.

I am keen to present my Editor's Pick for this publication, the article by AlDallal et al. which offers a review of 'Pregnancy-Related Thromboembolism in Sickle Cell Disease'. Hemoglobin disorders are predominant in tropical and subtropical countries where sickle cell disease and thalassaemias are frequently a major and challenging problem. This review encompasses the topics of genetic traits, pathology, associated health issues, pregnancy, venous thromboembolism, in addition to the management and treatment of sickle cell disease.

Pablo Martin offers another haematological review, this time with the focus on 'Initial Anticoagulant Management of Deep Vein Thrombosis/Venous Thromboembolism in Primary Care: Review of Current Approaches'. Martin herein discusses the long-established therapies, novel oral anticoagulants, and pathways in practice.

Furthermore, *EMJ Hematology* boasts a short review on the management of β-thalassaemia patients in the era of COVID-19, presented by Aggeli et al., and a case report on adult-onset Still's disease complicated with haemophagocytic lymphohistiocytosis, submitted by Asghar et al.

Abstract summaries from the virtual edition of the 25th European Hematology Association (EHA) Annual Congress, EHA25 Virtual, are also enclosed within these pages and are not to be missed. The complete congress review also features press releases from the congress on improved outcomes for amyloidosis patients treated with daratumumab, the promise of a hopeful treatment for steroid-refractory acute graft-versus-host disease, and the finding that omission of radiotherapy did not worsen survival in Hodgkin lymphoma.

Please sit back and enjoy the contents of this eJournal. I am already looking forward to receiving the submissions for our next issue!

Prof Emili Montserrat
University of Barcelona, Spain

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AML: acute myeloid leukaemia; **AML-MRC:** AML with myelodysplasia-related changes; **t-AML:** therapy-related AML

***High-risk AML defined as t-AML or AML-MRC**

1. Tolcher AW, Mayer LD. Future Oncol 2018; 14(13): 1317-32.
2. Lancet JE *et al.* J Clin Oncol 2018; 36(26): 2684-92.

Date of preparation: April 2020
INT-VYX-2000046

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Congress Review

Review of the European Hematology Association (EHA) Virtual Congress 2020

Location: EHA25 Virtual 2020

Date: 11th June – 22nd June 2020

Citation: EMJ Hematol. 2020;8[1]:12-24. Congress Review.

FRANKFURT am Main, Germany, more commonly referred to as Frankfurt, is known for its futuristic skyline and houses the busiest German airport, which is also the fourth busiest in Europe. The city is the financial capital of mainland Europe, home to the European Central Bank (ECB) and the Frankfurt Stock Exchange. For these reasons, Frankfurt is no stranger to international attention and serves as an ideal venue to host a world-leading congress. However, as a result of the COVID-19 pandemic, the physical 25th European Hematology Association (EHA) Congress, scheduled June 11–14th 2020 in Frankfurt, was replaced by a virtual meeting (11th–22nd June). Although attendees did not land at Frankfurt am Main Airport, traffic control provided clearance to land at EHA25 Virtual, providing an exhilarating 10-day congress experience from the comfort and safety of our homes.

Twenty-five years of the EHA annual congress have meant 25 years of inspiring innovations and scientific results contributing to EHA's annual congress evolving into the premier haematology congress in Europe. The Opening Ceremony was hosted by EHA President Prof John Gribben, Barts Cancer Institute, London, UK, who first commented on how COVID-19 has not only stopped the physical congress but also made EHA rethink the organisation of this and future congresses. "This crisis should not and will not stop us from sharing knowledge," he proclaimed before thanking the attendees for joining the innovative virtual edition of the 25th congress.

Following the Welcome Ceremony, Prof Gribben introduced the EHA 2020 winner of the José Carreras Award, established to honour leaders in clinical and translational haematology research. This is awarded every year to a recognised and active investigator who has made a significant contribution to the field of haematology. This year's winner, Prof Gilles Salles, University of Lyon, France, is a respected figure in the treatment of lymphomas. Prof Salles delivered a lecture on "Follicular

Lymphoma from Genetics to The Clinic," providing an overview of how follicular lymphoma develops in patients and how to choose optimal treatment options. Further honoured for his contributions to haematology was Prof Radek Skoda, University Hospital Basel, Basel, Switzerland, recipient of the David Grimwade Award, who delivered a lecture on "Clonal Evolution of Myeloproliferative Neoplasms."

Although held online, EHA still managed to provide a fantastic and effortless congress experience. The congress programme was split into on-demand and live sessions, including plenary presentations and symposia, and a regular theme-of-the day programme. Themes included acute leukaemia, coagulation disorders, lymphoma, and red and white cell disorders. Coupled with overview presentations, Q&A panel discussions, and a modern virtual exhibit hall, the experience was like no other.

As always, EHA has brought its audience a plethora of significant breakthroughs in the field. We are proud to present reports on some of this cutting-edge research over the next few pages. Topics span from improved outcomes for patients with amyloidosis using daratumumab, a patient group urgently requiring novel therapies; to achieving blood cell transfusion independence in patients with lower-risk myelodysplastic syndromes. These stories and more are described in the following pages. Our topical article covering "Coagulopathy and Hyperinflammation in COVID-19," based on the EHA three-part session on "COVID-19 and Hematology", will no doubt be of particular interest.

Here you will also find summaries of some of the finest abstracts presented at EHA, written by the authors themselves, providing a first-hand account into the research. Erkeland et al. detail the effects of reactivation of *MIR139* on *MLL-AF9* acute myeloid leukaemia, with results indicating that both *miR139* expression, or inactivation of *miR139* targets, eliminate *MLL-AF9* acute myeloid leukaemia. Ionova et al. focus on the quality of life of patients with haematological malignancies and demonstrate that the Haematological Malignancies Patient-Reported Outcome (HM-PRO) measure, developed by the EHA Scientific Working Group, is a valuable tool in capturing the patient's needs regardless of the state and stage of the disease.

It is tremendously exciting to gain a better understanding of the planning of a congress and the valuable work provided by the committees. Complementary to the congress coverage are informative interviews with the EHA Chair of the European Board for Accreditation in Hematology, EHA Chair Curriculum Committee, and the EHA Chair Guidelines Committee. The icing on the cake is our panel interview with two aspiring haematologists from the YoungEHA Committee, catering to the upcoming haematologists among you.

EHA25 Virtual presented a scientific programme of first-rate quality and immense variation, living up to its title as the premier haematology congress in Europe. It was inspiring to see how much the organisation has grown since being founded in 1992. We hope you take the time to indulge in the following pages and we look forward to seeing you at the 26th Congress of EHA in Vienna, Austria.

EHA 2020 REVIEWED →

Improved Outcomes for Patients with Amyloidosis with Daratumumab

ESTIMATED to have an incidence of 3–12 cases per million population annually, there are currently no health authority-approved therapies for light-chain (AL) amyloidosis. However, a recent clinical trial has reported success in treating patients with AL amyloidosis with the subcutaneous cluster of differentiation (CD)38-directed antibody drug daratumumab, traditionally used to treat multiple myeloma, in combination with cyclophosphamide-bortezomib-dexamethasone (CyBorD). This was announced in a press release at EHA25 Virtual on 12th June 2020.

"The primary endpoint of haematologic complete response rate was 53% for D-CyBorD compared to 18% for CyBorD."

A rare multisystem disorder that can become fatal, AL amyloidosis presents in patients whose bone marrow produces abnormal pieces of antibodies that accumulate into clumps called amyloid. These clusters are deposited in tissues and vital organs, interfering with normal bodily function.

The Phase III ANDROMEDA study compared daratumumab plus CyBorD (D-CyBorD) with CyBorD alone in patients diagnosed with AL amyloidosis. Here, 388 participants were eligible for the study, as determined by measurable haematologic disease, ≥1 involved organ, estimated glomerular filtration rate ≥20 mL/minute, and absence of symptomatic multiple myeloma.

The primary endpoint of haematologic complete response rate was 53% for D-CyBorD compared to 18% for CyBorD. Analysis of the 6-month response rate for patients treated with D-CyBorD for cardiac and renal responses were 42% and 54%, respectively, compared to 22% and 27%, respectively, for CyBorD.

Additionally, D-CyBorD was shown to have an acceptable safety profile, consistent with previous studies on daratumumab or CyBorD alone. Systemic administration-related reactions with D-CyBorD, mostly arising during the first infusion, occurred in 14 patients (7%), though all were Grade 1–2.

The deeper and more rapid haematologic responses observed with D-CyBorD, combined with improved clinical outcomes and an acceptable safety profile, highlight the promise of this treatment option for patients with AL amyloidosis, who are in urgent need of novel therapies.

Omission of Radiotherapy Does Not Worsen Survival in Hodgkin Lymphoma

RADIOTHERAPY could be avoided in young patients with Hodgkin lymphoma (HL), as positron emission tomography (PET)-guided chemotherapy protocols provide equally good tumour control as combined therapy. While combined therapy has been the standard care for patients with early-stage unfavourable HL for several decades, a European study has shown no worsening of tumour control with omission of radiotherapy.

Patients with risk factors suggesting an unfavourable prognosis despite early-disease HL are usually treated with a four-cycle protocol of combined chemoradiotherapy. However, as median age at disease onset is 30 years, the use of radiotherapy poses long-term risk of developing secondary malignancies or cardiovascular disease.

The European prospective, randomised trial of 1,100 patients assessed the impact of omitting radiotherapy compared to combination chemoradiotherapy, led by PET assessment of treatment response. The study altered the usual chemotherapy regimen of combined therapy (four cycles of ABVD) to two cycles of eBEACOPP and two cycles of ABVD ('2+2' therapy). There was no reduced tumour control without radiotherapy treatment in those patients responding well to chemotherapy. The study also identified that most patients respond well to chemotherapy and benefit from the radiotherapy-free treatment strategy.

Longer term outcomes were encouraging, with very high survival rates. Of the 1,100 patients enrolled, one death from HL and one death from treatment-related adverse events were reported. The mortality rate for the patients matched the control group; however, there was more severe haematological toxicity and infections with the new chemotherapy-alone regimen.

"The vast majority of early stage unfavourable HL patients can be treated with the brief and highly effective 2+2 chemotherapy alone," outlined Prof Peter Borchmann, German Hodgkin Study Group (GHSG), Cologne, Germany in his presentation of the study's findings at EHA25 Virtual. The long-term value of avoiding radiation exposure and the very high survival rates mean that this omission of radiotherapy is now considered the standard of care for the GHSG.

COVID-19 Treatment Prioritisation Required for Adult Haemoglobinopathy Patients

ADULT patients with the severe inherited blood disorders sickle cell disease (SCD) and thalassaemia could be at risk of experiencing severe outcomes from COVID-19. National data collected by the newly launched National Haemoglobinopathy Panel (NHP) were analysed by researchers at Queen Mary University of London, London, UK and outlined in a EHA25 Virtual press release dated 13th June 2020.

The survey of 199 patients with SCD and 26 patients with thalassaemia revealed that most confirmed and suspected cases of COVID-19, as classified by the World Health Organization (WHO) surveillance criteria, were mild. There was no associated increased risk in paediatric patients; however, adults with SCD appeared to be at increased risk of adverse outcomes of the virus. Cases included in the study were reported up to 5th June 2020.

The National Health Service (NHS) recently commissioned regional care networks across England to provide improved support and specialised services for haemoglobinopathy patients. These networks, overseen by the NHP, have accumulated clinical data collected throughout the spread of COVID-19 to quickly determine the associated level of risk for patients.

"For adults with SCD, isolation precautions should be lifted cautiously, and they should be prioritised for new therapies and vaccination when available," explained Dr Paul Telfer, Queen Mary University of London, Barts Health NHS Trust, London, UK. Identifying and quantifying the risk profile of this subgroup of patients with SCD or thalassaemia may allow for more targeted approaches to their care, and more specific considerations for reducing their risk of exposure to the infection. This study demonstrated the value of obtaining real-time data to evaluate risks faced by different patient groups during the COVID-19 pandemic.

"For adults with SCD, isolation precautions should be lifted cautiously, and they should be prioritised for new therapies and vaccination when available."

Novel C3 Complement Inhibitor Treatment for Paroxysmal Nocturnal Haemoglobinuria

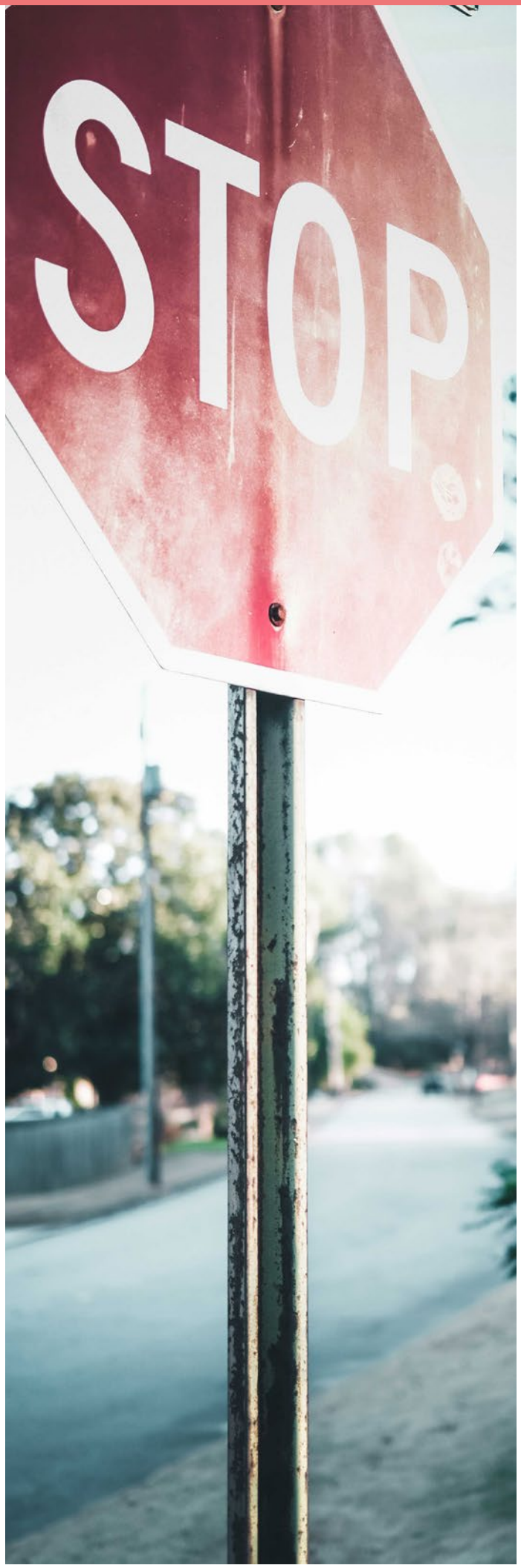
PEGCETACOPLAN, a new investigational drug for the treatment of paroxysmal nocturnal haemoglobinuria (PNH), has shown to be more effective than eculizumab in the resolution of anaemia according to a new study presented in a press release at EHA25 Virtual on 12th June 2020.

PNH is a rare but severe disease, affecting the blood cells and making them more fragile and prone to premature death by parts of the innate immune system. Here, the complement system attacks the cells, resulting in fatigue and severe anaemia. Often the patient will pass red or black urine as a result of intravascular and extravascular haemolysis, require blood transfusions, and experience dyspnoea and severe life-threatening blood clots in critical organs including the liver.

Eculizumab, a complement component 5 (C5) inhibitor, is the current standard treatment for PNH and although beneficial, many patients remain anaemic, fatigued, and require transfusion. As a result, the PEGASUS study aimed to find a more effective treatment option. The trial consisted of a 4-week run-in period to assess baseline values, followed by a 16-week randomised controlled period divided into the pegcetacoplan and eculizumab arm. Primary endpoints were analysed at Week 16.

PEGASUS is the first randomised Phase III trial of a proximal C3 inhibitor and the results showed that pegcetacoplan is considerably more effective than eculizumab in improving haemoglobin and other key disease markers in patients with PNH. Results highlighted pegcetacoplan's superiority to eculizumab for change in haemoglobin levels from baseline at Week 16 and the haemoglobin increase was maintained in all patients. After Week 16, all patients continued pegcetacoplan monotherapy to Week 48.

The safety profile of pegcetacoplan was comparable to that of eculizumab and, coupled with its superior treatment effects, these results demonstrate the potential for pegcetacoplan to control haemolysis in patients with PNH, making it a prospective new therapy option for patients with PNH.



Hopeful Treatment for Steroid-Refractory Acute Graft-Versus-Host Disease

"Median overall survival in the ruxolitinib group was almost twice as long as the control group, at 11.1 months compared to 6.5 months, respectively."

ALLOGENEIC stem-cell transplantation has the major limitation of patients developing acute graft-versus-host disease (GVHD), and some patients are refractory to steroid treatment. Results from the REACH2 Phase III trial, revealed in a press release at EHA25 Virtual on 11th June 2020, have shown that the drug ruxolitinib can improve the outcomes of refractory patients with the disease.

Ruxolitinib is a selective inhibitor of JAK1 and JAK2 and is a medication used to treat myeloproliferative neoplasms. In the multicentre, randomised, open-label REACH2 trial, the efficacy of oral ruxolitinib (10 mg twice daily) was compared against nine commonly used treatment options. A total of 309 patients participated; all were ≥12 years old and had undergone allogeneic stem-cell transplantation and subsequently developed glucocorticoid-refractory acute GVHD.

At Day 28, the primary endpoint of overall response (complete response or partial response) was higher in the ruxolitinib group than the control group, at 96 patients compared to 61, respectively (odds ratio [OR]: 2.64; 95% confidence interval [CI]: 1.65–4.22; p<0.001).

At Day 56, the key secondary endpoint of durable overall response was again higher in the ruxolitinib group than the control group, at 61 patients compared to 34 (OR: 2.38; 95% CI: 1.43–3.94; p<0.001). Estimation of cumulative incidence of loss of response at 6 months was deemed to be 10% for the ruxolitinib group and 39% for the control group, a stark contrast.

Median overall survival in the ruxolitinib group was almost twice as long as the control group, at 11.1 months compared to 6.5 months, respectively. However, thrombocytopenia had an increased incidence in the ruxolitinib group, with 33% of the 152 patients presenting with this adverse event, compared to 18% in the control group.

Despite the increased presentation of toxic side effects, the observed significant improvement in efficacy outcomes proves ruxolitinib to be the first novel agent to demonstrate superiority to standard therapy in patients with steroid-refractory acute GVHD in a Phase III trial.

Better Treatment Responses with Combination Therapy for Acute Myeloid Leukaemia

LIMITED treatment responses are often experienced with the standard commonly used lower-intensity therapies for acute myeloid leukaemia (AML). The combination regimen of azacitidine and venetoclax in patients with treatment-naïve AML has shown good efficacy in results from a Phase III trial presented at EHA25 Virtual, reported in a press release dated the 13th June 2020.

The median age of diagnosis for AML is 68–72 years, meaning that AML is primarily a disease of older adults. A median survival of 9–10 months and complete remission (CR)/CR with incomplete count recovery (CRi) rates <40% are commonly experienced with lower-intensity treatment regimens, for example azacitidine or decitabine alone. These limited responses can be attributed to medical comorbidities and high-risk disease-related biology in older adults.

VIALE-A is an ongoing, Phase III, randomised, double-blinded, multicentre trial investigating the efficacy of the combination of azacitidine and venetoclax in patients with treatment-naïve AML who were ineligible for intensive therapy. Those included were either ≥75 years of age or were 18–74 years with at least one of the predefined comorbidities, for example, chronic stable angina. Study participants (N=431) were randomised 2:1 to receive either the combination of azacitidine and venetoclax or azacitidine and placebo, respectively. The combination regimen of azacitidine and venetoclax resulted in an improved overall survival (14.7 versus 9.6 months) and improved response rates CR/Cri (66% versus 28%) compared with azacitidine alone. Additionally, a quicker response was associated with the combination regimen (median time to CR/Cri was 1.3 versus 2.8 months) and these responses were more durable (lasting 17.5 versus 13.4 months). An increased incidence of transfusion independence was also seen with the combination regimen (58% versus 34%).

Overall, the combination of azacitidine and venetoclax for patients with treatment-naïve AML extended survival in comparison with azacitidine and placebo. The results from this trial could pave the way for a new standard of care for older patients with AML.

Red Blood Cell Transfusion Independence Using Imetelstat

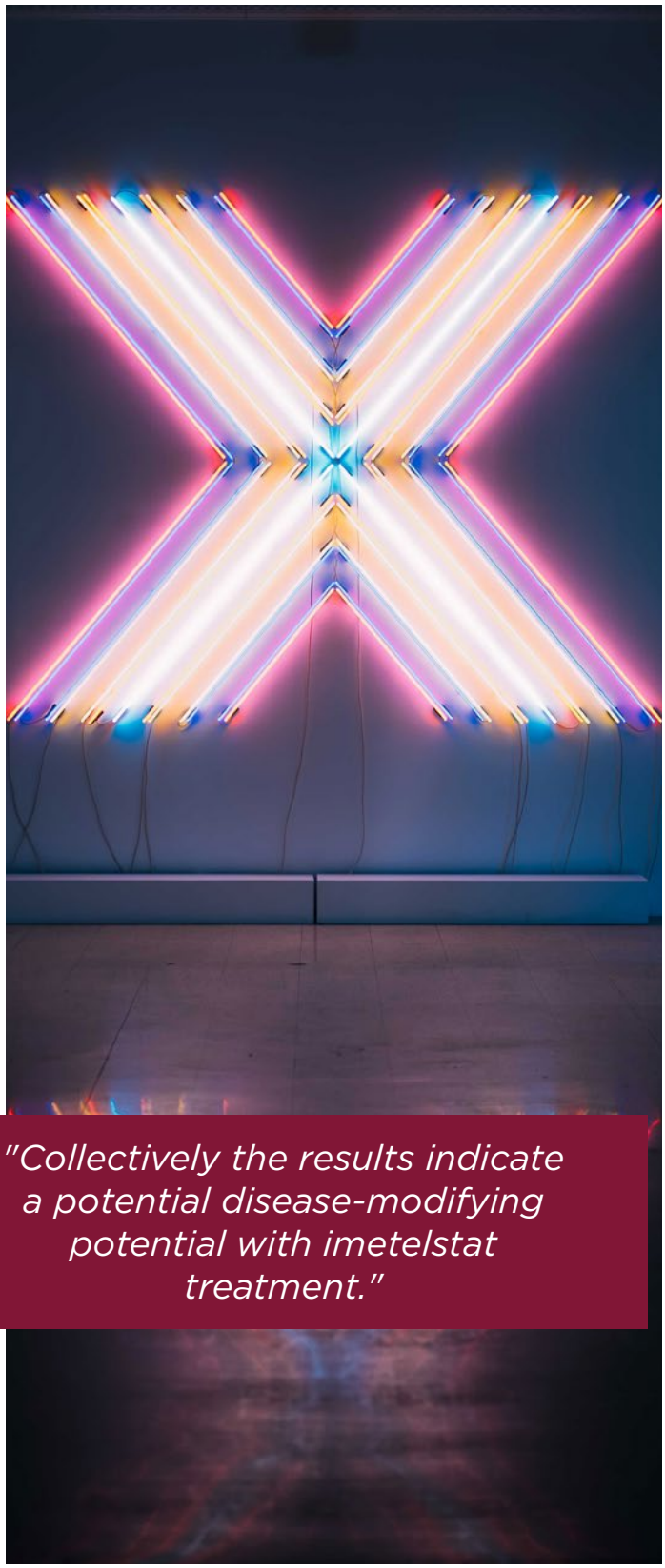
TRANSFUSION therapy, used in the treatment of patients with lower-risk myelodysplastic syndromes (LR-MDS), is an essential part of haematology practice. The results of the IMerge study were recently presented in a press release at EHA25 Virtual on the 12th June 2020 and report long-term efficacy with imetelstat to achieve 8-week red blood cell transfusion independence (RBC-TI).

Currently, patients with transfusion-dependent LR-MDS have limited treatment options; however, studies have shown that higher telomerase activity, expression of human telomerase reverse transcriptase, and shorter telomeres are risk factors for shorter overall survival in LR-MDS patients. Imetelstat is a potent competitive telomerase inhibitor that targets cells with short telomere lengths and active telomerase.

IMerge is a Phase II/III clinical trial evaluating imetelstat as a treatment option for LR-MDS patients (non-*del[5q]* MDS) that are dependent on red blood cell transfusion and relapsed after or are refractory to treatment with erythropoiesis-stimulating agents. The primary endpoint of the IMerge Phase II trial was to achieve 8-week RBC-TI, defined as the proportion of patients not receiving any RBC transfusion during any consecutive 8 weeks since starting the trial.

Of the 38 patients recruited, results highlighted long-term efficacy and overall safety. Imerge Phase II data showed that 16 patients (42%) achieved 8-week RBC-TI, and 12 of these responders (75%) experienced a haemoglobin rise compared to pretreatment during the transfusion-free interval. Furthermore, 12 patients (32%) achieved a 24-week RBC-TI and 11 patients (29%) were transfusion-free for >1 year.

This trial reported a median RBC-TI duration of 88 weeks, the longest reported to date in non-*del(5q)* LR-MDS, and collectively the results indicate a potential disease-modifying potential with imetelstat treatment. Ultimately, the most reported adverse events (reversible cytopenia) were not frequent and imetelstat showed promising treatment results that may help eliminate transfusion dependency for patients with LR-MDS, something that will be further evaluated in the currently recruiting, ongoing Phase III IMerge trial.



"Collectively the results indicate a potential disease-modifying potential with imetelstat treatment."

Pembrolizumab Improves Progression-Free Survival in Transplant-Ineligible Hodgkin Lymphoma

LIMITED treatment options for transplant-ineligible patients with chemorefractory Hodgkin lymphoma have been broadened by evidence that pembrolizumab increases progression-free survival. A Phase III study has compared safety and efficacy of pembrolizumab to brentuximab vedotin, and found superior progression-free survival with pembrolizumab.

"A Phase III study has compared safety and efficacy of pembrolizumab to brentuximab vedotin, and found superior progression-free survival with pembrolizumab."

Transplant ineligibility in Hodgkin lymphoma may result from chemorefractory disease, age, or comorbidities. While the standard of care for relapsed, refractory Hodgkin lymphoma is salvage chemotherapy and autologous stem cell transplantation, for those ineligible for transplant there is no standard of care. The Italian Phase III study KEYNOTE-204 compared pembrolizumab (n=81), a PD-1 inhibitor, to brentuximab vedotin (n=88) in patients who had relapsed after, or were ineligible for, autologous stem cell transplant.

The study found a statistically significant increase in progression-free survival with pembrolizumab treatment. Median progression-free survival for the patients treated with pembrolizumab monotherapy was 13.2 months versus 8.3 months for those treated with brentuximab vedotin (hazard ratio: 0.65; 95% confidence interval: 0.48–0.88; p=0.00271). The benefits of pembrolizumab treatment extended to those patients in subgroups of primary refractory disease and those who had not received a previous autologous stem cell transplant.

The findings of this Phase III trial were presented at EHA25 Virtual. Dr Pier Luigi Zinzani, Institute of Haematology "L. e A. Seràgnoli", University of Bologna, Bologna, Italy outlined his view of the impact of the study on the treatment paradigm for Hodgkin lymphoma: "Pembrolizumab should be considered the preferred treatment option and new standard of care for the treatment of relapsed/refractory classical Hodgkin lymphoma in patients who have relapsed after autologous stem cell transplant or are ineligible for auto-SCT."

Biologic Therapy for Hereditary Haemorrhagic Telangiectasia

HEREDITARY haemorrhagic telangiectasia (HHT), also known as Osler-Weber-Rendu disease, is the second most common blood disorder worldwide and has a prevalence of 1 in 5,000. Currently no U.S. Food and Drug Administration (FDA)-approved therapy exists; however, a new study has evaluated intravenous bevacizumab and considers it a potential standard treatment option for HHT patients. These findings were reported in a press release at EHA25 Virtual on 12th June 2020.

HHT patients are affected by chronic gastrointestinal bleeding and severe recurrent epistaxis that results in chronic and often severe iron deficiency anaemia. To maintain safe blood counts, patients generally depend on blood transfusions and iron infusions. Furthermore, HHT results in elevated levels of vascular endothelial growth factor (VEGF); therefore, existing VEGF-targeting medication may be effective in the treatment of HHT.

In the multicentre retrospective study InHIBIT-Bleed, Dr Hanny Al-Samkari and his team, Massachusetts General Hospital, Boston, Massachusetts, USA, evaluated the efficacy of intravenous bevacizumab. Bevacizumab, a bioengineered VEGF-targeting antibody, was used in 238 patients with HHT to treat bleeding for a median duration of 1 year.

The study measured haemoglobin levels, epistaxis, and red cell transfusion and iron infusion requirement before and after bevacizumab initiation. The results showed that 67% of patients anaemic at baseline achieved freedom from anaemia, 92% achieved a clinically meaningful reduction in Epistaxis Severity Score (ESS), 80% were red blood cell transfusion-free after 6 months of treatment, and 61% were iron infusion-free after 6 months of treatment.

Treatment was safe and no fatal treatment emergent adverse events were recorded. These results highlight that existing VEGF-targeting medication hold promise for effective treatment of bleeding in HHT and should be evaluated in future studies. Collectively, the study proved that bevacizumab is a safe and effective biologic therapy option to treat bleeding in patients with HHT.

"These results highlight that existing VEGF targeting medication hold promise for effective treatment of bleeding in HHT and should be evaluated in future studies."

"Allogenic haematopoietic stem cell transplant (HSCT) cures approximately 50–80% of paediatric ALL patients, making it one of the most powerful leukaemia therapies."

Total Body Irradiation Benefits Conditioning for Stem Cell Transplantation

SUCCESSFUL treatment for acute lymphoblastic leukaemia (ALL) in patients aged <18 years is achieved in >90% of cases using contemporary chemotherapy. However, for the remaining 10% there are lasting effects from the conditioning process of the alternate treatment regimen. In the ALL SCTped FORUM trial, the possibility of not including total body irradiation (TBI) in the conditioning was explored, but this trial was terminated early because of the significantly better results of the standard approach. Results from this study were presented at EHA25 Virtual and in a press release dated 12th June 2020.

For the 10% of patients with ALL who have resistant or recurring leukaemia, alternative treatment regimens are needed. Allogenic haematopoietic stem cell transplant (HSCT) cures approximately 50–80% of paediatric ALL patients, making it one of the most powerful leukaemia therapies. There are five main steps in the allogenic HSTC procedure: 1) identify a suitable donor; 2) reduce the patient's leukaemia to an undetectable level; 3) harvest haematopoietic stem cells from the donor; 4) condition the patient for transplantation; 5) transplant the stem cells.

Sterility, growth retardation, pulmonary issues, and secondary cancer are highly negative consequences of the conditioning step of allogenic HSCT, despite its efficacy to control the leukaemia. A global study, FORUM, was launched to investigate whether chemotherapy-based conditioning could substitute TBI. Patients (N=413) were aged 4–21 years, and only those in complete remission were eligible. Lower overall survival rates were experienced in the chemotherapy-based conditioning compared with the standard combination of TBI and chemotherapy, leading to the trial being terminated early.

Although FORUM was not a positive trial, much was learnt during the process, such as the feasibility and efficacy of national and international collaboration and that there were no differences between the two chemo-conditioning groups (busulfan- or treosulfan-based). Many questions remain, and the researchers are now performing prospective monitoring to facilitate better defined advantages and limitations of a collection of conditioning approaches.

Coagulopathy and Hyperinflammation in COVID-19

Katherine Colvin
Editorial Assistant

Citation: EMJ Hematol. 2020;8[1]:25-28.

MORTALITY in novel coronavirus disease 2019 (COVID-19) is impacted by haematological complications and therefore, addressing these may improve patient survival. In shared presentations at the 25th European Hematology Association (EHA) Annual Congress, expert haematologists discussed clinical and scientific findings in the global experience of severe acute respiratory syndrome coronavirus-2 (SARS-CoV-2) infection, analysed data to articulate current understanding, and provided insights for care and management of affected patients. The final stage of a three-part programme was a presentation titled "Treatment of COVID-19: Current and Future", which included detailed examinations of thrombosis management, immunotherapy, and the value of haematologists' expertise in combatting this current pandemic.

COVID-19, a disease resulting from SARS-CoV-2 infection, generally results in mild-to-moderate illnesses in those affected. However, 15% of symptomatic patients develop severe interstitial pneumonia, with 5% going on to develop profound and life-threatening complications including acute respiratory distress syndrome, sepsis, hyperinflammatory syndromes, and multiorgan failure. Clinical complications of COVID-19 include myocarditis, acute myocardial infarction, heart failure, venous thromboembolism, and cerebrovascular events. These vascular and thromboembolic complications suggest a coagulopathic impairment requiring specialist haematological examination and input.

THROMBOSIS

COVID-19-Associated Hypercoagulopathy

In contrast to the typical disseminated intravascular coagulation (DIC) pattern seen in trauma or bacterial sepsis, COVID-19 is associated with a clinical coagulopathy but mild thrombocytopenia and minimal prolongation of the activated partial thromboplastin time or prothrombin time. In her presentation to the virtual congress, Prof Anna Falanga, of the University of Milano-Bicocca, Milan, Italy and Hospital Papa Giovanni XXIII, Bergamo, Italy, outlined the coagulopathy seen in patients infected with SARS-CoV-2: "What is really interesting is that in this infection, there is a clear association of D-dimer levels with the severity of the disease." Prof Falanga went on to discuss findings across several international studies

where a consistent association of D-dimer levels with both severity of infection and poorer prognosis has been observed. However, she noted that great variability in the D-dimer levels has been reported between studies. Similarly, platelet levels have been associated with disease severity but reported levels vary between studies.

In her analysis of the currently available body of evidence, Prof Falanga went on to discuss the coagulation markers in patients in intensive care, with a pattern of results more consistent with a hypercoagulability of a severe inflammatory state, rather than acute DIC. In the pathogenesis of this hypercoagulability, the severe inflammatory state seen with COVID-19 causes a profound derangement of the haemostatic system. The impact of the cytokine storm, the hyperinflammatory host immune response triggered by SARS-CoV-2, leads to direct tissue damage, secondary tissue damage from shock states, acute respiratory distress syndrome, and multiorgan failure. The inflammatory cytokines also promote massive infiltration of the lung tissue by neutrophils and macrophages and activate blood clotting. This activation of blood clotting occurs by cytokines inducing activation of vascular endothelium, platelets, and leukocytes, resulting in dysregulation of thrombin generation. Excessive thrombin generation, with subsequent fibrin formation, has both a systemic and local lung effect in the setting of severe pneumonia, where deposition of fibrin leads to direct tissue damage and to microangiopathy.

Viral Effects on the Endothelium

In her discussion of the pathophysiology of COVID-19, Prof Falanga elaborated on the mechanisms of action and direct effects of SARS-CoV-2. SARS-CoV-2 can also interact with the endothelium directly, causing microvascular dysfunction and leading to organ ischaemia. SARS-CoV-2 also exploits the angiotensin-converting enzyme receptor-2 to infect host cells. As this receptor is expressed on endothelial cells across multiple organs, the multiorgan complications of SARS-CoV-2 can be partly explained by the direct effect of the virus on the endothelium by way of this receptor. This interaction leads to immune cell recruitment which can trigger systemic endothelial dysfunction, shifting the balance of the vasculature toward vasoconstriction, and leading to organ ischaemia, tissue oedema causing further inflammation, and a procoagulant state. Prof Falanga emphasised the research findings supporting this understanding; the inflammation-associated endothelial changes directly triggered by SARS-CoV-2 are supported in autopsy studies of patients, revealing the presence of viral elements within endothelial cells and diffuse endothelial inflammation.

The hypercoagulability seen in COVID-19 is a consequence of the inflammatory response to severe infection but is also a consequence of the direct effect of SARS-CoV-2 on the endothelium. The severity of coagulation derangement is

associated with poorer prognosis in affected patients. Prof Falanga discussed a retrospective study that has shown that prophylactic low-molecular-weight heparin is associated with a reduction in mortality risk; as a result, it is currently recommended by multiple scientific societies, including the International Society on Thrombosis and Haemostasis (ISTH) and Italian Society for the Study of Hemostasis and Thrombosis (SISET), as well as by the World Health Organization (WHO).

"...treatment of the underlying infection remains the primary intervention for improving coagulopathy in COVID-19."

Venous Thromboembolism

The coagulopathy seen in COVID-19 is also demonstrated through evidence of venous thromboembolism (VTE) in affected patients. Prof Falanga continued her presentation by examining the published body of evidence. She noted that there are conflicting data on the incidence of VTE in patients with COVID-19; rates range from 0–8% in general medical wards to 16–35% in patients in intensive care units, with VTE events often occurring in the presence of adequate low-molecular-weight heparin prophylaxis. In autopsy studies, a VTE incidence rate of up to 58% has been identified in patients with COVID-19 where VTE was not suspected prior to death. A larger study comparing data from 1,765 patients across multiple studies found that VTE occurred in approximately 20% of patients with COVID-19; cumulative incidences were noted to be up to 49% in cases of hospitalisation. A post hoc meta-analysis of this study determined that the proportion of VTE occurrance is much greater in patients in intensive care, and that there is both publication bias and heterogeneity of data affecting the validity of these findings.

Prof Falanga went on to discuss the mechanisms involved in VTE in patients with COVID-19. The VTE events in COVID-19 resulting in pulmonary vessel occlusion could result from macrothrombosis via embolisation of deep-venous thrombosis, or from microthrombosis via thrombotic microangiopathy of the pulmonary vascular bed. It has been postulated that the diffuse, bilateral pulmonary inflammation seen in COVID-19 causes a localised microangiopathy, distinct from DIC; this novel, pulmonary-specific pathophysiological process has been termed pulmonary intravascular coagulopathy. Autopsy studies have revealed platelet–thrombin microthrombi in the lungs, which is consistent with a coagulopathy process.

The coagulopathy processes of COVID-19, resulting from both severe inflammation and direct effects of SARS-CoV-2 on the endothelium, contribute to the severity of illness, incidence of complications, and mortality risk of COVID-19. Algorithms for determining correction of coagulopathies and use of prophylactic low-molecular-weight heparin have been proposed by published studies, but further assessment into the outcomes of such interventions is required. Prof Falanga closed her presentation by reiterating that treatment of the underlying infection remains the primary intervention for improving coagulopathy in COVID-19.

IMMUNOTHERAPY

There are two immunotherapeutic strategies by which haematological expertise can help to address COVID-19, as discussed by Prof Hermann Einsele, Medical Clinic and Polyclinic II at the University Hospital Centre for Internal Medicine, Würzburg, Germany. Prof Einsele outlined an early immunotherapy strategy, making use of convalescent plasma to improve clearance of the virus and improve infection outcomes, and a late immunotherapy strategy, which aims to reduce the hyperinflammatory syndrome of life-threatening COVID-19.

The first Nobel Prize in Physiology or Medicine, awarded to Emil Behring in 1901, recognised the use of convalescent plasma therapy. Prof Einsele reviewed the available evidence on the use of convalescent plasma therapy for patients with COVID-19. Currently, its use in COVID-19 remains investigational, with data mostly limited to case reports and further study needed. One randomised controlled trial of 103 patients undertaken in China found that, based on viral nucleic acid PCR testing, 33.3% of patients

"...the best strategy for preventing life-threatening complications and COVID-19-associated deaths is early treatment of the viral infection itself, an area of ongoing global effort."

receiving convalescent plasma had cleared the viral infection at 24 hours, compared to 11.8% without the plasma therapy. At 72 hours, 90.5% of patients in the plasma group had cleared the virus, compared to 41.2% of those in the control group. The time to clinical improvement was not significantly different between the two groups overall or within the subset of patients classed as having life-threatening disease, although patients with clinically severe disease improved at a faster rate when receiving convalescent plasma therapy. However, Prof Einsele emphasised that this study did not standardise therapy for COVID-19, which may have impacted the reliability of the results.

Peripheral blood screening has revealed evidence of the hyperinflammatory state associated with COVID-19. In a further review of the published global evidence, Prof Einsele explained that the pattern of change in inflammatory profiles maps to clinical severity; a low lymphocyte count and low platelet count in the early phase of infection is associated with a more severe infection and worse outcome. Similarly, high C-reactive protein, IL-6, IL-1, lactate dehydrogenase, creatine kinase, and ferritin in the early phase of the infection are each associated with severe disease. Other patterns emerging in published research were highlighted by Prof Einsele in his presentation to the congress. CT imaging in COVID-19 cases links the severity of hyperinflammation and cytokine release measured by blood testing with the severity of pulmonary infiltration on imaging. Secondary haemophagocytic lymphohistiocytosis (sHLH) can occur with severe COVID-19 and lead to fulminant hypercytokinaemia, multiorgan failure, and death; pulmonary involvement occurs in approximately 50% of patients with sHLH. Hallmark features of sHLH include hyperferritinaemia, fever, and cytopenias, which are also recognised in severe COVID-19 infection. This further suggests that mortality in COVID-19 may relate to virally driven hyperinflammation. In addressing this hyperinflammation, reduction in viral load has been found to improve inflammatory markers.

Prof Einsele went on to consider possible avenues of treatment for these processes of hyperinflammation and associated poorer clinical outcomes. The increased activation of Th1 cells and inflammatory monocytes seen in COVID-19, more pronounced in life-threatening infection, could potentially be addressed with tocilizumab or anakinra immunotherapy. Prof Einsele noted that previous experience with CAR T-cell therapy in oncology has revealed a typical cytokine release syndrome with high fevers and high inflammatory reactions; in oncological and haematological pathologies, this cytokine release syndrome is treated with tocilizumab. Tocilizumab may, therefore, be a potential treatment strategy in COVID-19 to address pathogenic T cell- and inflammatory monocyte-mediated hyperinflammation.

CONCLUSION

Severe infection and life-threatening complications in COVID-19 result, in part, from a substantial hyperinflammatory response and cytokine cascade, generating a coagulopathy and contributing to mortality. Addressing coagulopathy with blood product management, microangiopathy and thromboembolism risk with low-molecular-weight heparin prophylaxis, and hyperinflammatory syndromes with immunotherapy agents are all late-stage interventions, using haematological expertise to minimise mortality risk in the sickest patients. Using patterns of inflammatory markers and coagulation profiles to risk-stratify patients for early intervention may help mitigate this risk earlier in the disease course. However, the best strategy for preventing life-threatening complications and COVID-19-associated deaths is early treatment of the viral infection itself, an area of ongoing global effort.

Doing More for Patients with Immune Thrombocytopenia: Putting New Recommendations into Practice

This symposium took place on 11th June 2020, as part of the virtual 25th European Hematology Association (EHA) Annual Congress

Chairperson: Aristoteles Giagounides[1]

Speakers: Aristoteles Giagounides,[1] John Grainger,[2] Drew Provan,[3] Maria L. Lozano[4]

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Meeting Summary

The latest developments in treatment recommendations and new management strategies for patients with immune thrombocytopenia (ITP) were highlighted at this symposium. There is a renewed focus on improving not only clinical outcomes such as bleeding, but also quality of life (QoL) for patients with ITP, as well as increased recognition of the importance of patient involvement in their treatment decision making. Thanks to an expanding body of clinical data and better understanding of the underlying disease pathogenesis, the concept of tailoring ITP treatment to individual patients is becoming a reality. Therapies such as thrombopoietin receptor agonists (TPO-RA) play an important role in this transformation of patient management. TPO-RA are recommended for use in ITP based on robust clinical evidence, and during the COVID-19 pandemic their importance as nonimmunosuppressive therapies has been highlighted in several guidelines. Generally in newly diagnosed patients with ITP, nonimmunosuppressive therapies such as intravenous Ig (IVIG) and TPO-RA are recommended over corticosteroids,[1-4] and for patients with chronic ITP it is suggested to not make any alterations to therapy.[1,2]

Some TPO-RA already have a range of licensed applications outside of ITP, such as myelodysplastic syndrome (MDS) and chemically induced thrombocytopenia. Their full potential is still under investigation and promising preliminary clinical studies have indicated that TPO-RA may have therapeutic applications in other diseases.

Using ASH Guidelines and ICR Recommendations to Guide Clinical Decisions

Professor John Grainger

The American Society of Hematology (ASH) guidelines and the International Consensus Report (ICR) recommendations were first published in 2010[5] and 2011,[6] with updates presented in December[7] and November 2019,[8] respectively. In this period, new clinical evidence and treatments for ITP became available and both the ASH and ICR recommendations have incorporated these updates to present a comprehensive framework for ITP patient management.

The importance of QoL for patients and individualisation of treatment via patient involvement in decision making is given new weight in the updated publications. In the ICR recommendations, treatment goals are individualised to the patient and phase of disease and the maximisation of QoL features is the treatment aim, alongside prevention of severe bleeding, providing safe platelet levels, and minimising toxicity.[8] In the ASH guidelines, patient values and preferences are considered when selecting second-line therapies.[7]

In both updates there is now an emphasis on moving away from immunosuppressive therapies. Corticosteroids remain the standard first-line therapy, but their use in short courses (<6 weeks) only is recommended.[7,8] TPO-RA are not considered as initial therapies in either the ASH guidelines or the ICR recommendations,[7,8] and rituximab is only suggested as an adjunct to corticosteroids in specific cases in the ASH guidelines.[7]

With respect to second-line therapies in adults, both the ICR recommendations and ASH guidelines advocate the earlier use of TPO-RA (as soon as 3 months after diagnosis).[7,8] The ICR recommendations indicate that there is robust evidence for the use of TPO-RA, fostamatinib,[9] and rituximab as second-line therapies (Figure 1). These should be used in preference to splenectomy, which should generally be deferred for adults who have been diagnosed with ITP for >1 year.[8] In the ASH guidelines, the recommendation for adults with ITP of >3 months is to use either a TPO-RA (romiplostim or eltrombopag) or rituximab, with splenectomy suggested as an option after 12 months. Rituximab is preferred over splenectomy and TPO-RA over rituximab, although the ASH guidelines focus on patient values in this setting and defer to patient preference for which therapy is given.[7]

For paediatric patients with ITP, both the ICR recommendations and ASH guidelines focus on bleeding scores for guiding treatment decisions and suggest observation of newly diagnosed patients who have no or mild bleeding. In more severe cases of bleeding, short courses of corticosteroids are recommended as initial treatment.[7,8] The ICR also recommends IVIG if a rapid increase in platelet count is required,[8] but the ASH guidelines take a more conservative approach to the use of IVIG in this setting, recommending preferential use of corticosteroids.[7]

With respect to persistent or chronic ITP, the ICR recommendations note that paediatric patients with stable platelet counts can be managed with observation, corticosteroids, and IVIG as rescue therapy for acute bleeding. TPO-RA are preferred in cases of persistently low platelet counts based on the number of clinical studies demonstrating good responses, reduction in bleeding frequency, improved QoL, and a good safety profile. In cases of lack of response to first-line therapy in paediatric patients, the ASH guidelines recommend TPO-RA in preference to either splenectomy or rituximab, but acknowledge the importance of patient preference in the overall selection of therapy.[7] In those who fail to respond to TPO-RA, especially adolescent females, the ICR recommendations suggest rituximab plus dexamethasone as an alternative option.

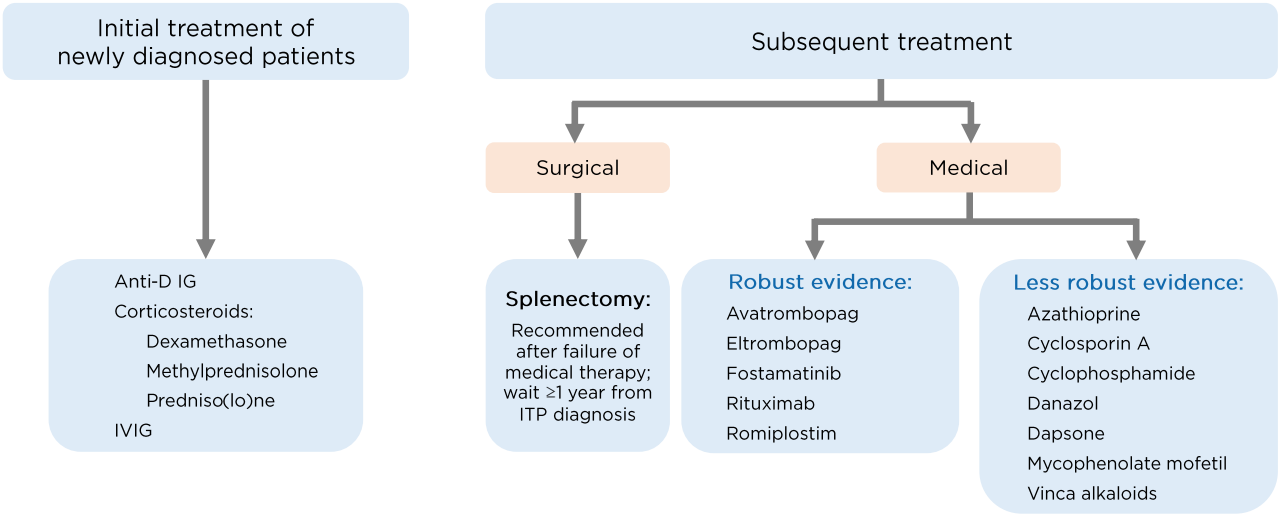


Figure 1: Treatment of immune thrombocytopenia in adults according to the International Consensus Report (ICR) recommendations.

IVIG: Intravenous Ig; ITP: immune thrombocytopenia.

Adapted from Provan D et al.[5]

If response to a TPO-RA is lost, adding mycophenolate mofetil or an alternative immunosuppressant, or switching to another TPO-RA, may be considered.[8]

Thrombopoietin Receptor Agonists in the New ICR Recommendations: Improving Treatment Strategies

Professor Drew Provan

In the 10 years since the first ICR recommendations were published, the use of TPO-RA in clinical practice has dramatically increased and they are now widely used to treat patients with ITP. The updated ICR recommendations reflect this increase in use and provide detail on the most appropriate use of TPO-RA in clinical practice.

Adult Patients

Whilst the approved starting dose of romiplostim is 1 µg/kg per week,[10] the average weekly romiplostim dose in most studies is 3–5 µg/kg, and more than one study has used 3 µg/kg as the starting dose.[11-13] Platelet responses are typically seen within 2 weeks,[14,15] and lengthened dose intervals for romiplostim have not been shown to be effective.[16] The approved dose of eltrombopag is 25–75 mg/day, with the daily dose decreased for platelet counts >200×10^9/L.[17,18] TPO-RA provide excellent responses in both splenectomised and nonsplenectomised patients; in an integrated analysis of romiplostim in 1,111 patients with ITP, platelet responses were seen in 82% and 91% of patients with and without splenectomy, respectively.[19] Responses have been monitored in clinical studies for up to 6–8 years, often allowing other ITP therapies to be reduced or discontinued. A good example of this is seen in the EXTEND study, an open-label extension study for patients with ITP receiving eltrombopag. Platelet counts increased rapidly over the first 2 weeks of treatment and were maintained over the duration of the study (250 weeks).[20,21]

A patient starting TPO-RA therapy often asks whether the treatment will be lifelong. Although cessation of TPO-RA treatment leads to a return of thrombocytopenia in many cases, some patients may achieve a durable response after withdrawal of a TPO-RA. In a Phase II single-arm study, remission was demonstrated in 32%

of patients with ITP who received romiplostim within 6 months of diagnosis.[11] In another study, 28% of patients with chronic ITP who received romiplostim for >6 months achieved remission.[22] Treatment-free remission has also been seen with eltrombopag; in one retrospective study, 53% of evaluable patients with ITP who responded to eltrombopag sustained a response for ≥6 months after discontinuation.[23]

Failing multiple therapies is a common problem that worries clinicians and patients. This issue is addressed in the ICR recommendations. If a patient fails to respond to a TPO-RA, switching from one TPO-RA to another can be considered; this has shown a positive effect on response and tolerability.[24-27] One study has shown switching TPO-RA to be effective in 50–80% of patients, with eradication of platelet fluctuations in 54% of patients and resolution of adverse events in all patients.[24] The ICR also noted that the addition of small doses of corticosteroids to prior lines of therapy should be explored in patients who have failed multiple therapies.[8]

Emergency treatment is required when patients sustain severe bleeding or to reduce the risk of sudden bleeding. According to the ICR recommendations, a combination of treatments, including IV corticosteroids and IVIG, should be used in emergency situations. Platelet transfusions may also be helpful. In the case of life-threatening bleeding and the absence of a significant response to the above options, TPO-RA may be considered.[8]

Paediatric Patients

TPO-RA are recommended in chronic or persistent ITP in children, and this recommendation is supported by multiple clinical studies. In a key Phase III randomised, double-blind study of romiplostim in children, a durable platelet response of 52% and an overall response of 71% was demonstrated.[28] In the paediatric ITP setting, these figures are good. As for adult patients, switching TPO-RA is also recommended if response to a TPO-RA is lost.[8]

Tailoring Immune Thrombocytopenia Treatment to the Individual

Professor Maria L. Lozano

Personalising management for patients with ITP is important, although there are challenges in optimising therapeutic strategies. For patients who receive treatment for their ITP, despite diverse pathophysiological differences, treatment strategies are often very similar. Consequently, some patients respond better to treatment than others. In an ideal world, in order to better tailor ITP treatment to the individual, management should be differentiated based on underlying disease mechanism and biological characteristics (Figure 2).

New clinical data in first-line therapy of ITP could potentially guide and tailor treatment decisions. According to current guidelines, corticosteroids are the mainstay of initial ITP treatment,[7,8] but which newly diagnosed patients require steroid treatment and which steroid and dose to use are both important questions. The consensus is to initiate therapy in patients who experience bleeding or have a low platelet count, but a recent publication sought to provide granularity as to who is most at risk of bleeding and, therefore, would most benefit from corticosteroid treatment. The relationship between different factors and haemorrhagic manifestations was studied in 20,000 adult patients with a new diagnosis of ITP in a Japanese registry. Results indicated that previous haematuria, platelet count $<15\times10^9$/L, and age >60 years were relevant contributors to an increased risk of bleeding.[29] In terms of which corticosteroid to initiate, a meta-analysis has shown that dexamethasone works faster than prednisolone in terms of complete response at 14 days, and with a similar safety profile.[30] Because sustained remission rates were similar at 6 months, either agent was deemed appropriate, but, in the absence of contraindications, responses to dexamethasone may be more rapid. With respect to steroid dosing, for elderly patients or those with underlying diseases and a high or higher probability of adverse events, doses of <1 mg/kg of prednisolone may be more suitable.

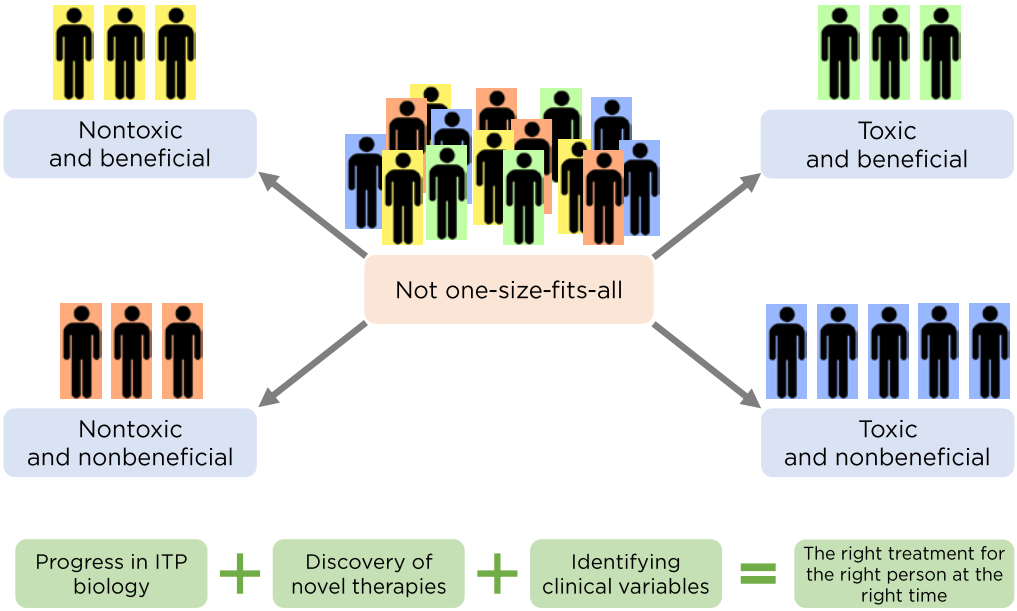
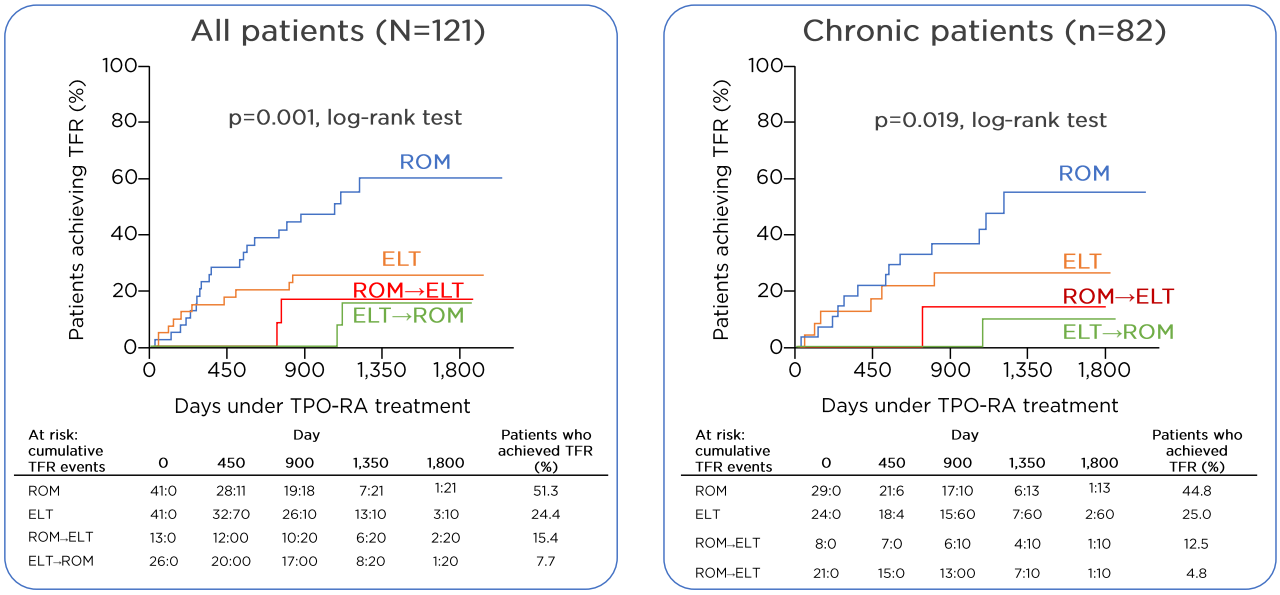


Figure 2: Principles behind tailoring treatment to individual patients.

ITP: immune thrombocytopenia.

Courtesy of Prof Lozano.



At risk: cumulative TFR events	Day 0	450	900	1,350	1,800	Patients who achieved TFR (%)
ROM	41:0	28:11	19:18	7:21	1:21	51.3
ELT	41:0	32:70	26:10	13:10	3:10	24.4
ROM–ELT	13:0	12:00	10:20	6:20	2:20	15.4
ELT–ROM	26:0	20:00	17:00	8:20	1:20	7.7

At risk: cumulative TFR events	Day 0	450	900	1,350	1,800	Patients who achieved TFR (%)
ROM	29:0	21:6	17:10	6:13	1:13	44.8
ELT	24:0	18:4	15:60	7:60	2:60	25.0
ROM–ELT	8:0	7:0	6:10	4:10	1:10	12.5
ROM–ELT	21:0	15:0	13:00	7:10	1:10	4.8

Figure 3: Treatment-free response in immune thrombocytopenia with thrombopoietin receptor agonists.

ELT: eltrombopag; ROM: romiplostim; TFR: treatment-free response; TPO-RA: thrombopoietin receptor agonist.

Adapted from Lozano ML et al.[33]

Since patients with ITP are at increased risk of thrombosis, and some ITP therapies contribute to this risk, it would be valuable to be able to identify patients who may develop this complication.[31,32] A retrospective study of 7,225 patients with ITP in France identified several risk factors for arterial thrombosis and venous events in patients undergoing splenectomy. Age, male sex, previous arterial thrombosis, and exposure to antiplatelet drugs were associated with arterial thrombosis, and age, cancer, and a history of venous thromboembolism were related to venous events.[31]

Regarding appropriate selection of second-line therapies, a recently published retrospective analysis evaluated the use of TPO-RA in adults with ITP. This found that, in clinical practice, severity of ITP is a key factor in the choice of TPO-RA. At the time of ITP diagnosis and on the day of TPO-RA initiation, bleeding symptoms were more frequent and more severe, and platelet counts were significantly lower among patients who were assigned to romiplostim.[33] With respect to rituximab, small retrospective studies have indicated that females in the early phases of ITP (rituximab plus dexamethasone)[34] or >40 years of age[35] seem to have the highest probability of sustained response. In a recently published study assessing the long-term efficacy and safety of rituximab,[36] again, women >40 years of age seemed to have the best response. However, there were no significant differences in response with respect to sex. Considering splenectomy, and whether surgery or medical therapy is most appropriate for long-term management of ITP, it is important to discuss the risks and benefits of splenectomy with patients, and to actively encourage their participation in treatment decisions.

There is currently no single approach for the management of multirefractory patients. The best management approach may not be to administer single agents in a sequential manner, but rather to consider combination therapy, targeting multiple pathways by which thrombocytopenia can occur. In addition, recent incorporation of new treatments such as TPO-RA mean that some patients with chronic ITP may now be able to achieve treatment-free responses (TFR). In a retrospective study, 51% of patients who received romiplostim without subsequent TPO-RA switching were able to sustain a TFR upon discontinuation of therapy.

The number of patients achieving TFR with eltrombopag (24%) appeared to plateau after the first year, but the number of patients achieving TFR progressively increased over time in the case of romiplostim. These results still need to be validated but are an indication that a high number of patients may be able to achieve TFR with medical therapy alone (Figure 3).[33] Prof Lozano also noted that high response rates and good safety profiles of TPO-RA make these agents especially beneficial for elderly patients with ITP, who experience a high frequency of serious bleeding and an inherently high thrombotic risk.

Thrombopoietin Receptor Agonists Beyond Immune Thrombocytopenia

Professor Aristoteles Giagounidis

TPO-RA have been investigated in several settings outside of ITP and chemotherapy-induced thrombocytopenia, for example in aplastic anaemia (AA) and MDS.

Aplastic Anaemia

At presentation, virtually all patients with AA have severe thrombocytopenia. The consequences of this can be severe or even life-threatening, for example in cases of intracranial haemorrhage. Current treatment typically consists of platelet transfusions whilst awaiting a response to immunosuppression or haematopoietic stem cell transplantation. However, TPO levels are typically elevated in AA, suggesting a therapeutic role for TPO-RA in this setting.[37-39] Clinical studies with TPO-RA in patients with AA have indicated that both romiplostim and eltrombopag can improve haematological responses in this setting. A Phase II/III study was undertaken to investigate romiplostim in patients with AA who were ineligible or refractory to immunosuppressive therapy. A haematological response was seen in 84% of patients at 27 weeks, trilineage responses were seen in 26% of patients, and the median time to any haematological response was 37 days.[40] Another study with romiplostim in 35 patients with AA investigated platelet responses over a longer period. Platelet response rate was 36% at Week 27, which was well maintained up to Week 105 (30%).[41] Eltrombopag was also

investigated in a seminal study of 43 patients with AA; at 12–16 weeks, 40% of patients had (any) haematological response and at the last follow-up (median 12 months), 16% had a trilineage response.[42,43]

Myelodysplastic Syndrome

Despite the incidence of severe thrombocytopenia in MDS only being 7–19%, it is still of concern because it indicates poor prognosis. Bleeding is also the second most common cause of death in MDS after sepsis.[44-48] Management of thrombocytopenia in patients with MDS may include platelet transfusions, IVIG, steroids, and disease-modifying agents such as azacitidine or decitabine.[49-51] TPO is elevated in MDS, again suggesting the potential for TPO-RA as therapy in this setting. In several Phase II studies, TPO-RA were found to have a positive effect on platelet counts and, in some cases, reduced the requirement for platelet transfusions. Romiplostim has been studied in patients with lower-risk MDS in a Phase II placebo-controlled study: in patients with platelet levels ≥20–50×10^9/L, the number of bleeding events was significantly reduced ($p<0.0001$), and in patients with platelet levels <20×10^9/L, the number of platelet transfusions was significantly reduced compared with placebo ($p<0.0001$). However, there was no difference in overall survival.[52] The Phase II EUROPE study investigated endogenous TPO levels and their predictive power in patients with low-risk MDS receiving romiplostim. Response rates were higher in patients with lower TPO levels and in patients who had pretreatment transfusion needs of <6 units in the past year. However, despite romiplostim being more effective in this subgroup of patients, neither platelet transfusion requirement nor TPO levels were significantly associated with response.[53] Eltrombopag has been investigated in 90 patients with low-risk MDS, low platelet counts, and receiving supportive care. Eltrombopag had a significantly increased response rate versus placebo (47% versus 3%; $p=0.0017$).[54]

Conclusion

Over the last few years, the development of targeted therapies and emergence of new clinical data have enhanced outcomes for patients with ITP. This has opened the door to the possibility of individualisation of treatment, a concept now recognised in the updated ICR recommendations and ASH guidelines. Individualisation of treatment and greater consideration for patients' QoL are the cornerstones of contemporary management strategies in ITP. TPO-RA play an important role in this new management paradigm, as supported by the updated ICR recommendations and ASH guidelines. Mutual participation in treatment decisions between patients and physicians is also recognised, and this collaborative approach to treatment should be integral when putting these new recommendations into clinical practice. TPO-RA have already been demonstrated to have promising applications outside of ITP and have even further potential in the treatment of other diseases in the future.

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Outcomes for Patients with High-Risk Acute Myeloid Leukaemia: Can We Move from Months to Years?

The symposium and poster presentations took place on 11th June 2020 as part of the 25th European Hematology Association (EHA) Annual Congress.

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Meeting Summary

This symposium and the accompanying poster presentations focussed on high-risk acute myeloid leukaemia (AML). The speakers discussed the recognition of, and treatment options for, patients with high-risk disease based on clinical studies and real-world data. Prof Cluzeau described how high-risk AML is defined as AML with myelodysplasia-related changes (AML-MRC) and therapy-related AML (t-AML). Patients with high-risk AML have a poor prognosis. The approach to AML therapy has not changed substantially in recent years, relying on intensive chemotherapy and allogeneic stem cell transplantation (alloSCT). However, therapies such as Vyxeos® Liposomal ([Jazz Pharmaceuticals, Dublin, Ireland] generic name: CPX-351), the first dual drug, advanced liposomal formulation of daunorubicin and cytarabine, 44 mg/100 mg powder for concentrate for solution for infusion, has been approved in Europe for the treatment of newly diagnosed AML-MRC or t-AML. Prof Russell

explained that long-term survival is achievable and alloSCT is the treatment of choice, with early recognition of high-risk disease and optimisation of induction therapy enabling more patients in complete remission (CR) access to alloSCT. As pretransplant minimal residual disease (MRD) status is an important determinant of transplant outcome, MRD measurements postinduction can help identify high-risk patients who are otherwise in CR and may benefit from alloSCT. Dr McLornan highlighted that identifying high-risk features of AML at diagnosis is mandatory for prognosis and therapeutic stratification. Long-term data with Vyxeos Liposomal in the 301 Phase III study confirmed significant improvements in overall survival (OS), including post-transplant. The exploratory, post hoc analysis from the 301-study presented by Dr Lin et al. showed that Vyxeos Liposomal improved median OS versus the 7+3 regimen in patients who achieved CR, or CR with incomplete haematologic recovery (CRi) but did not undergo alloSCT. The 5-year results from the 301 study presented by Dr Lancet et al. showed that improved OS with Vyxeos Liposomal versus the 7+3 regimen was maintained in the overall study population, in patients who achieved CR or CRi and in those who underwent alloSCT. Thus, Vyxeos Liposomal contributed to long-term remission and survival in older patients with newly diagnosed high-risk AML.

Introduction

This symposium focussed on the recognition of, and treatment options for, high-risk AML. Prof Cluzeau considered universal or targeted treatment and where the focus should be, Prof Russell addressed whether high-risk AML can be cured, and Dr McLornan discussed laying the foundations for long-term remission.

Universal or Targeted Treatment of Acute Myeloid Leukaemia: Where Should the Focus Be?

Professor Thomas Cluzeau

Prof Cluzeau explained that high-risk AML is defined by the 2016 World Health Organization (WHO) classification as AML with MRC and therapy-related myeloid neoplasms.[1] Approximately one-third (24–35%) of all AML cases are AML-MRC and this is predominantly observed in elderly patients.[2] AML-MRC is defined as the absence of both prior cytotoxic therapy for an unrelated disease and recurring cytogenetic abnormality.[1,3]

Three entities for AML-MRC have been identified.[1,3] Firstly, AML post-myelodysplastic syndrome (MDS) or post-MDS/myeloproliferative neoplasm (MPN) is defined by prior MDS[1] or prior MDS/MPN,[1] with at least 6 months of prior disease history of MDS or MDS/MPN (Cluzeau T., personal clinical experience). Secondly, for *de novo* AML with MDS-related cytogenetic abnormalities,[1] the WHO classification gives a list of cytogenetic abnormalities sufficient to diagnose AML-MRC when ≥20% peripheral blood or bone marrow blasts are present and prior therapy has been excluded. The list includes complex karyotype (three or more abnormalities), unbalanced abnormalities, and balanced abnormalities. Thirdly, in AML with multilineage dysplasia, dysplasia must be present in >50% of cells in at least two bone marrow cell lines and no *NPM1* mutation or biallelic *CEBPA* mutation.[1]

Approximately 7% of all cases of AML are t-AML.[4] Risk for t-AML is associated with alkylating agent, radiation therapy, and topoisomerase II inhibitor treatment.

Prof Cluzeau described that AML-MRC had significantly reduced OS and progression-free survival and lowered CR rate compared with other forms of AML (p=0.001).[5] In t-AML with a higher prevalence of *TP53* mutations and a complex karyotype, prognosis was relatively poor.[6] Secondary AML (s-AML) without MDS also had a poor prognosis; t-AML and s-AML (secondary to MDS) had similar prognoses, and all three were associated with a poorer prognosis than *de novo* AML.[7]

Prof Cluzeau reviewed the European Leukemia Net (ELN) treatment option recommendations for the high-risk AML-MRC and t-AML subgroups.[4] Treatment for patients who are eligible for intensive chemotherapy is based on induction therapy combining anthracycline and cytarabine, followed by consolidation therapy using

chemotherapy or chemotherapy plus alloSCT in patients with intermediate-risk or adverse-risk genetics. For patients who are not eligible for intensive chemotherapy, agents such as azacitidine and decitabine are usually recommended, but low-dose cytarabine or best supportive care can be used in some patients.

Four therapeutic regimens for AML have been approved by the European Medicines Agency (EMA): Vyxeos Liposomal (daunorubicin and cytarabine 44 mg/100 mg; approved August 2018)[8] as intensive chemotherapy and Rydapt® ([Novartis Pharmaceuticals Corporation, Basel, Switzerland] generic name: midostaurin; September 2017),[9] Mylotarg™ ([Pfizer Inc., New York City, New York, USA] generic name: gemtuzumab ozogamicin; April 2018),[10] and Xospata® ([Astellas Pharma, Tokyo, Japan] generic name: gilteritinib; October 2019)[11] as targeted therapy.

Prof Cluzeau introduced Vyxeos Liposomal as a therapeutic option in AML-MRC and t-AML, presenting the improved median OS versus the 7+3 cytarabine/daunorubicin regimen, including a significant increase in median OS in patients who underwent alloSCT.[12]

Prof Cluzeau concluded that patients with high-risk AML, defined as AML-MRC or t-AML, have a poor prognosis.[7] The general approach to AML therapy has not changed substantially in recent years, relying on intensive chemotherapy and alloSCT;[4] however, therapies have been approved in Europe for the treatment of specific patient subgroups.[9,11] Tailoring treatment through identification of high-risk groups such as AML-MRC and t-AML has a beneficial therapeutic impact.[12]

Can High-Risk Acute Myeloid Leukaemia Be Cured?

Professor Nigel Russell

Prof Russell explained that the prognosis and relative survival of patients with high-risk AML becomes progressively worse with age, particularly in patients aged >65 years for whom 5-year relative survival is <20%.[13] High-risk AML can be recognised at diagnosis in patients who have an adverse risk karyotype[4] or adverse genomics[4,14] and in patients with a history of s-AML,[4] previous antecedent myeloid dysplasia, or t-AML. High-risk status may be indicated after first induction, with the presence of an adverse genotype or primary refractory disease.[14] Following second induction, high risk is indicated in patients who have not achieved CR or CR with CRi, and those who have MRD.[14] Haematological or molecular relapse also indicates high risk.[14]

Prof Russell outlined recent experience in the UK of the National Cancer Research Institute (NCRI) trials in younger patients (aged 15–59 years) with high-risk AML, focussing on patients with adverse-risk cytogenetics, which is one of the hallmarks of high-risk disease. Examining sequential trials (AML 10 [1988–1994], AML 12 [1994–2002], AML 15 [2002–2009], and AML 17 [2009–2016]) showed the improving prognosis for these patients; however, <20% of patients were cured in the follow-up period to 2015.[15]

The strategy for high-risk AML in the UK NCRI trials included recognising high-risk patients early,[4] rapid diagnostics, cytogenetics and mutational analysis,[15] and using MRD both as an early response indicator of risk status and an early signal of impending relapse.[4,15] Prof Russell considered the challenge of high-risk AML as three-fold. Firstly, improving pretransplant chemotherapy could reduce post-transplant relapse rate.[16] Secondly, better treatment could deliver more patients to transplant who otherwise might not have remitted or relapsed before undergoing alloSCT.[16] Thirdly, more effective treatments are needed for patients for whom alloSCT is not an option.[4,15]

In patients with *NPM1*^{mut} AML, MRD measurement post-course 2 can identify high-risk disease.[17] Postinduction MRD in peripheral blood also predicts outcome and benefit from alloSCT in *NPM1*^{mut} AML.[18] Furthermore, pretransplant MRD measurement can predict patients at high risk of relapse. Presence of MRD in patients who have achieved CR is associated with similarly poor outcomes with patients who have active disease pre-alloSCT, showing the importance of absence of MRD prior to alloSCT.[19-21] Pre-alloSCT MRD transcript measurements can predict post-transplant outcome.[22]

Prof Russell concluded that long-term survival is achievable in high-risk AML and that alloSCT is

the treatment of choice. Early recognition of high-risk disease and optimising induction therapy enables more patients to get to alloSCT in CR. Furthermore, MRD measurements postinduction can help identify high-risk patients who are otherwise in CR who may benefit from alloSCT.

Laying the Foundations for Long-Term Remission in High-Risk Acute Myeloid Leukaemia

Doctor Donal McLornan

Dr McLornan commented that advances in the understanding of the heterogeneity and molecular and cytogenetic knowledge of AML are increasingly used to guide therapeutic decisions. The goal of treatment in AML is to attain and maintain a first CR. AlloSCT is often used as postremission therapy for patients with normal and unfavourable karyotypes. The 10-year outcome of patients with AML not treated with alloSCT at a first CR is poor.[23]

The standard approaches to intensive therapy for AML for the last 45+ years have involved a 7+3 regimen.[24] As introduced by Prof Cluzeau, however, four novel drug regimens have been approved by the EMA: Vyxeos Liposomal,[8] Rydapt,[9] Mylotarg,[10] and Xospata.[11] Vyxeos Liposomal is the first licensed dual drug, advanced liposomal formulation of a fixed 1:5 molar ratio of daunorubicin and cytarabine, and is designed to optimise drug delivery to improve efficacy.[8,12,25,26] It is indicated for the treatment of adults with newly diagnosed AML-MRC or t-AML.[8]

Study 301 was a multicentre, randomised, open-label, Phase III study to compare Vyxeos Liposomal versus the 7+3 regimen in older adults with newly diagnosed high-risk/s-AML.[27-29] Key eligibility criteria were previously untreated AML, aged 60–75 years, ability to tolerate intensive AML chemotherapy, and Eastern Cooperative Oncology Group (ECOG) performance status (PS) 0–2. Patients received 1–2 cycles of induction, and those who achieved CR or CRi were allowed consolidation for 1–2 cycles. Primary and secondary endpoints were standard for a Phase III trial looking at remission, survival, and safety. A total of 309 patients were enrolled, with a mean age of 68 years, PS was mostly 0 or 1 and, as expected, cytogenetic risk groups were predominantly intermediate or poor; one in five patients in both cohorts had t-AML.[12]

In the primary endpoint analysis, Vyxeos Liposomal significantly increased median OS versus the 7+3 regimen (median follow-up: 20.7 months).[12,30] Median (95% confidence interval [CI]) OS was 9.56 (6.60–11.86) months for Vyxeos Liposomal versus 5.95 (4.99–7.75) months for the 7+3 regimen (p=0.003). There was a 31% reduction in risk of death for patients treated with Vyxeos Liposomal versus the 7+3 regimen (hazard ratio [HR]: 0.69; 95% CI: 0.52–0.90; p=0.003).[12]

There were significantly greater CR rates with Vyxeos Liposomal versus the 7+3 regimen (37% versus 26%, respectively; odds ratio [OR]: 1.69; 95% CI: 1.03–2.78; 2-sided p=0.040) and significantly greater overall remission rates (CR+CRi) versus the 7+3 regimen (48% versus 33%, respectively; OR: 1.77; 95% CI: 1.11–2.81; 2-sided p=0.016).[12] Overall remission rate (CR+CRi) after one induction cycle was 55.2% (58/105) with Vyxeos Liposomal versus 34.0% (34/100) with the 7+3 regimen.

Early mortality rates were lower with Vyxeos Liposomal than with the 7+3 regimen.[12,31] Sixty-day mortality caused by adverse events (AE) was comparable for Vyxeos Liposomal and the 7+3 regimen (10.4% versus 9.9%, respectively), and persistent or progressive disease caused this to be markedly lower for Vyxeos Liposomal than the 7+3 regimen (3.3% versus 11.3%, respectively).[31] Similar types of AE were recorded for the two treatments and were experienced by similar proportions of patients in each cohort.[12]

In the Vyxeos Liposomal arm, 49 and 23 patients underwent consolidation 1 and 2, respectively, compared with 32 and 12 patients, respectively, for the 7+3/5+2 regimen.[32] Importantly, from a physician and hospital perspective, 51% and 61% of patients received Vyxeos Liposomal consolidation 1 and 2 as an outpatient, respectively.[32]

Continued therapy with Vyxeos Liposomal throughout induction and consolidation improved OS compared with the 7+3/5+2 regimen. Median (95% CI) OS favoured Vyxeos Liposomal at 25.43 (12.35–not reached) months compared with 8.53 (5.68–15.21) months for the 7+3/5+2 regimen.[32]

A greater proportion of patients received alloSCT following Vyxeos Liposomal compared with the 7+3 regimen (52/153, 34% versus 39/156, 25%, respectively; 2-sided p=0.098).[12] The study arms were similar, but more patients were ≥70 years in the Vyxeos Liposomal arm (16/52, 31%) versus the 7+3 arm (6/39, 15%) and more patients on 7+3 required salvage therapy pretransplant (12/39, 31% versus 5/52, 10%, respectively).[12] Median OS landmarked from the date of alloSCT was not reached for Vyxeos Liposomal, compared with 10.25 (95% CI: 6.21–16.69) months for the 7+3 regimen. There were 53% fewer deaths within 100 days of transplant in those who received Vyxeos Liposomal versus the 7+3 regimen.[33]

The total number of patients achieving CR+CRi following induction was 73/153 (48%) with Vyxeos Liposomal versus 52/156 (33%) with the 7+3 regimen (p=0.016) and for CR was 37% versus 26%, respectively (p=0.040). These data equate to improved OS: median OS was longer with Vyxeos Liposomal (25.43; 95% CI: 13.01–not reached) versus the 7+3 regimen (10.41; 95% CI: 7.82–15.21) in patients who achieved CR or CRi.[34] Amongst patients who achieved CR or CRi and underwent alloSCT, median OS landmarked from the date of alloSCT was not reached for Vyxeos Liposomal and was 11.65 months for the 7+3 regimen (HR: 0.42; 95% CI: 0.20–0.86).[34] Results for patients who achieved CR or CRi but did not undergo alloSCT are presented below.[27]

Dr McLornan shared the 5-year final results of study 301, which were presented at the American Society of Clinical Oncology (ASCO) Annual Meeting and the European Hematology Association (EHA) Annual Congress, showing that the improved median OS with Vyxeos Liposomal versus the 7+3 regimen seen at 3 years was maintained (9.33 versus 5.95 months, respectively). Notably, for patients who underwent alloSCT with OS landmarked from the time of transplant, survival rate was 52% for Vyxeos Liposomal versus not estimable for the 7+3 regimen.[28,29] Dr McLornan emphasised that over one-half of patients who received Vyxeos Liposomal and then underwent alloSCT were still alive 5 years later, and that median OS landmarked from the date of alloSCT was not reached for Vyxeos Liposomal versus 10.25 months for the 7+3 regimen; therefore, stratification of therapy upfront is an optimal approach.

Dr McLornan concluded that identifying high-risk features of AML at diagnosis is mandatory for prognosis and correct therapeutic stratification. Long-term data with Vyxeos Liposomal in the 301 study[28,29] confirmed significant improvements in OS, including post-transplant.

Outcomes in Older Patients with High-Risk/Secondary Acute Myeloid Leukaemia Who Achieved Remission with CPX-351 Versus the 7+3 Regimen but Did Not Undergo Transplant: Phase III Exploratory Analysis

Doctor Tara L. Lin et al.

This exploratory, post hoc analysis of the 301 Phase III study evaluated outcomes in the subgroup of patients who achieved CR or CRi with CPX-351 versus the 7+3 regimen, but did not undergo alloSCT.[27] Patient baseline characteristics were generally balanced between treatment arms; however, in the CPX-351 arm, there were more males and patients with a PS of 1, but fewer patients with antecedent MDS, hypomethylating agent exposure, and PS 0 or 2, versus the 7+3 arm. Remission (CR+CRi) following induction was achieved in 73/153 (48%) patients with CPX-351 versus 52/156 (33%) with the 7+3 regimen. Amongst those attaining CR or CRi, 33/73 (45%) with CPX-351 and 28/52 (54%) with the 7+3 regimen did not subsequently undergo alloSCT.

Median OS (months) was longer with CPX-351 (14.72; 95% CI: 9.33–25.43) versus the 7+3 arm (7.59; 95% CI: 4.86–10.87) (HR: 0.57; 95% CI: 0.31–1.03) in patients who achieved CR or CRi but did not undergo alloSCT. Among patients aged 60–69 years, median OS was 15.74 months with CPX-351 versus 7.36 months with the 7+3 arm (HR: 0.53; 95% CI: 0.23–1.22) and among patients aged 70–75 years, median OS was 12.19 months with CPX-351 versus 8.41 months with the 7+3 regimen (HR: 0.47; 95% CI: 0.19–1.21).

Median time to recovery of neutrophils and platelets was longer with CPX-351 than with the 7+3 arm (35.0 and 36.0 days versus 29.0 and 28.5 days, respectively).

The AE profile for CPX-351 was generally similar to that of the 7+3 regimen, with febrile neutropenia, nausea, constipation, and diarrhoea being the most common AE.

The authors concluded that CPX-351 improved median OS versus the 7+3 regimen, irrespective of age in patients who achieved CR or CRi but did not undergo alloSCT, indicating a benefit, and potentially deeper response, with CPX-351 treatment in this subgroup.

Five-Year Results of a Phase III Study of CPX-351 Versus the 7+3 Regimen in Older Adults with Newly Diagnosed High-Risk/Secondary Acute Myeloid Leukaemia

Doctor Jeffrey E. Lancet et al.

Outcomes for the treatment of AML with the 7+3 regimen are particularly poor for older adults and those with high-risk-AML.[7,35,36] This prospectively planned, final follow-up of the 301 Phase III study evaluated patients until death or up to 5 years following randomisation to assess the longevity of the results, including significantly improved median OS, observed at the primary endpoint analysis.[12]

The final 5-year follow-up results (median follow-up: 60.65 months) from the 301 Phase III study (previously presented at the ASCO 2020 Annual Congress)[28] showed that improved median OS with CPX-351 versus the 7+3 regimen was maintained (9.33 versus 5.95 months, respectively; Kaplan–Meier OS curves plateaued at around 30 months), with an HR (0.70; 95% CI: 0.55–0.91) that was consistent with the previous primary endpoint analysis (0.69; 95% CI: 0.52–0.90)[12] and thus maintained for up to 5 years.[28,29] The Kaplan–Meier estimated survival rates were higher for CPX-351 versus the 7+3 arm at 3 years (21% versus 9%, respectively) and 5 years (18% versus 8%, respectively).

A total of 53/153 (35%) and 39/156 (25%) of patients in the CPX-351 and 7+3 arms, respectively, underwent alloSCT. Median OS landmarked from the date of alloSCT was not reached for CPX-351 versus 10.25 months for the 7+3 regimen. The Kaplan–Meier-estimated survival rate landmarked from the date of transplant was 52% at 5 years for patients treated with CPX-351.

CR or CRi was achieved by 73 (48%) patients with CPX-351 and 52 (33%) patients with the 7+3 regimen. Among these patients, median OS was longer with CPX-351 versus the 7+3 regimen and the Kaplan–Meier-estimated survival rate was higher for CPX-351 versus the 7+3 arm at 3 and 5 years. The authors concluded that improved OS with CPX-351 versus the 7+3 regimen was maintained at 5 years in the overall study population, in patients who achieved CR or CRi, and in those who underwent alloSCT.

Questions and Answers

Q: What Were the Key Results from Your Analysis of the Early Experience with Vyxeos Liposomal in France?

Prof Cluzeau highlighted the good safety profile of Vyxeos Liposomal, with less gastrointestinal and skin toxicity and alopecia than observed with the 7+3 regimen, and the increase in haematological toxicity was manageable.[37] There was a good CR rate and 72% of patients in CR had MRD $<10^{-3}$, indicating a deep response. Median OS in patients who underwent alloSCT was not reached.

Q: What Were the Key Results from the 5-Year Follow-Up of Vyxeos Liposomal Versus the 7+3 Regimen in Older Adults with Newly Diagnosed High-Risk/ Secondary Acute Myeloid Leukaemia?

Prof Russell explained that the survival advantage observed at 3 years with Vyxeos Liposomal was maintained, with a plateau from 3 to 5 years.[28,29] Median OS was significantly improved with Vyxeos Liposomal versus the 7+3 regimen, more patients achieved remission and underwent alloSCT and more patients went into remission post-alloSCT.

Q: What Does This Mean for Treatment of Newly Diagnosed High-Risk Acute Myeloid Leukaemia?

Dr McLornan emphasised correct therapeutic stratification upfront for the patient and the improved OS with Vyxeos Liposomal versus the

7+3 regimen, including post-transplant, with equivalent safety. Historically, remission rates are poor in this subgroup. Now, more patients are receiving alloSCT and survival >1 year is observed in patients who do not undergo alloSCT.

Conclusion

In conclusion, high-risk AML is "curable" with early recognition and correct therapeutic stratification upfront. Vyxeos Liposomal contributes to long-term remission and survival in older patients with newly diagnosed high-risk-AML. Integration of novel chemotherapy, targeted agents, and immunotherapeutic platforms is the future in transplantation and will improve patient survival. Further prospective studies[38] and new approaches are needed to target MRD both pre- and post-alloSCT to optimise outcomes for patients with high-risk AML.

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AGILE: Phase III, Double-Blind, Randomised, Placebo-Controlled Study of Ivosidenib in Combination with Azacitidine in Adults with Newly Diagnosed Acute Myeloid Leukaemia and an *IDH1* Mutation

This abstract was presented from 11th to 21st June 2020, as part of the Virtual 25th European Hematology Association (EHA) Congress

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Summary

Acute myeloid leukaemia (AML) commonly affects the elderly and is associated with a high risk of relapse and poor overall survival.[1] AML patients who are ineligible for standard therapy based on advanced age and/or comorbidities have poor prognosis and limited treatment options;[2,3] therefore, there is an unmet clinical need for certain subgroups of AML patients.

Isocitrate dehydrogenase 1 (IDH1) is a metabolic enzyme which catalyses the oxidative decarboxylation of isocitrate to α-ketoglutarate, while the mutant IDH1 (mIDH1) enzyme catalyses the reduction of α-ketoglutarate to the oncometabolite D-2-hydroxyglutarate.[4,5] Accumulation of D-2-hydroxyglutarate results in myeloid differentiation arrest and epigenetic dysregulation, promoting leukaemogenesis.[6-8] Somatic mutations in the *IDH1* gene occur in 6–14% of patients with AML.[9]

In an ongoing Phase Ib study,[10] 23 newly diagnosed patients with mIDH1 AML were treated with ivosidenib 500 mg once daily, in combination with azacitidine 75 mg/m^2 for 7 days (in a 28-day schedule). The spectrum of adverse events has been consistent with monotherapy experiences with ivosidenib or azacitidine. The investigators of the study reported four cases of IDH differentiation syndrome: three were deemed to be serious adverse events, but all four cases resolved.

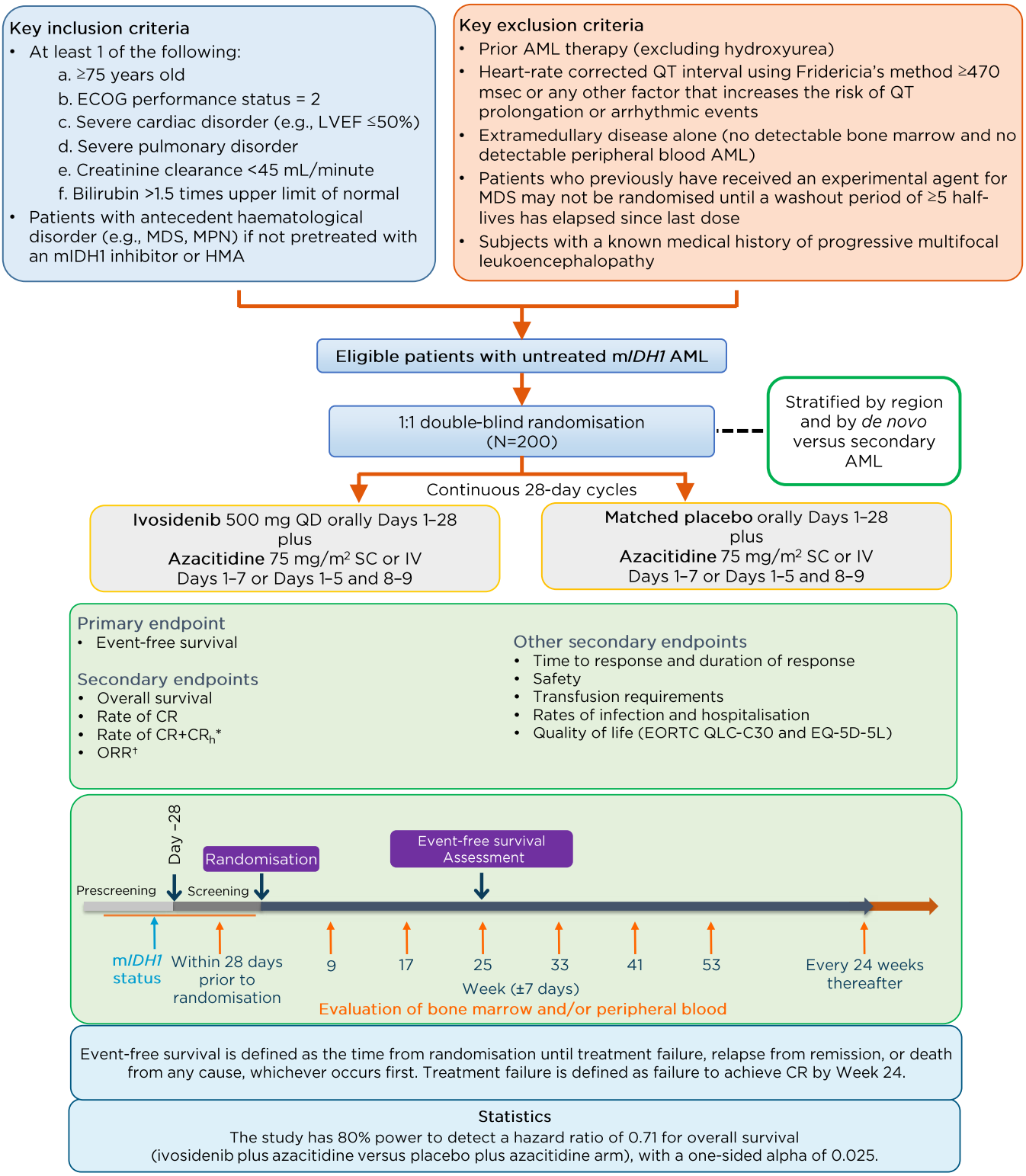

Figure 1: AGILE study schema.

*CR_h is defined as CR with partial recovery of peripheral blood counts (<5% bone marrow blasts, platelets >50,000 /µL, and ANC >500 /µL) and will be derived by the sponsor.

†Includes CR, CR_i/CR_p, partial response, and morphological leukaemia-free state.

AML: acute myeloid leukaemia; ANC: absolute neutrophil count; CR: complete remission; CR_h: complete remission with partial haematologic recovery; CR_i: complete remission with incomplete haematologic recovery; CR_p: complete remission with incomplete platelet recovery; ECOG: Eastern Cooperative Oncology Group; EORTC QLQ-C30: European Organization for the Research and Treatment of Cancer Quality of Life Questionnaire; EQ-5D-5L: EuroQol-5 dimension 5-level health-related quality of life questionnaire; LVEF: left ventricular ejection fraction; HMA: hypomethylating agent; IDH1: isocitrate dehydrogenase 1; IV: intravenous; MDS: myelodysplastic syndrome; m*IDH1*: mutant *IDH1*; MPN: myeloproliferative neoplasms; SC: subcutaneous; WHO: World Health Organization; QD: once daily.

Adapted from Montesinos et al.[12]

The overall response rate was 78.3% (18 patients) and 60.9% (14 patients) achieved a complete remission (CR). Median time to response was 1.8 months (range: 0.7–3.8 months) and median time to CR was 3.7 months (range: 0.8–15.7 months). Overall survival probability (12-month rate) was 82%. In patients with CR, mIDH1 clearance (<0.02–0.04%) in bone marrow mononuclear cells was observed in 71% (10 out of 14) of patients. These data provided the rationale for the design of the AGILE Phase III clinical trial.[11]

The authors report protocol amendments of key inclusion criteria and study design of the ongoing AGILE study of the ivosidenib plus azacitidine combination regimen in adults with mIDH1 newly diagnosed AML. AGILE is a global, double-blind, randomised, placebo-controlled, Phase III trial with a total of 166 participating study centres in North America, South America, Asia, and Europe. The study schema is shown in Figure 1.[12] Enrolled patients were randomised 1:1 to receive either a combination of ivosidenib 500 mg once daily plus azacitidine 75 mg/m^2 for 7 days in 28-day cycles, or a matched placebo plus azacitidine. Randomisation was stratified by region and by *de novo* versus secondary AML. Key eligibility criteria included patients with previously untreated mIDH1 AML, who were not candidates to receive induction chemotherapy (IC) treatment, and who had not received prior treatment with a hypomethylating agent or mIDH1 inhibitor. The recent amendment further specified criteria for IC-ineligibility as ≥75 years of age or reduced Eastern Cooperative Oncology Group performance status ([ECOG PS]: 2), or significant organ dysfunction (i.e., severe cardiac or pulmonary disorder, or impaired renal or liver function). The primary endpoint has been changed to event-free survival, defined as the time from randomisation until treatment failure, relapse from remission, or death from any cause (whichever occurs first). Treatment failure was defined as failure to achieve CR by Week 24. Key secondary efficacy endpoints were amended to overall survival, CR rate, CR plus CR with partial haematologic recovery rate, and overall response rate.

The favourable safety profile and encouraging clinical activity observed in the Phase Ib ivosidenib plus azacitidine combination study for the treatment of IC-ineligible mIDH1 AML warrant a timely and accurate assessment of the clinical benefit in this difficult-to-treat population with the Phase III AGILE clinical trial. AGILE is currently open for enrolment globally.

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Phase Ib/II Study of the IDH1-Mutant Inhibitor Ivosidenib, with the BCL2-Inhibitor Venetoclax +/-Azacitidine in *IDH1*-Mutated Myeloid Malignancies

This oral presentation was presented on 12th June 2020, as part of the Virtual 25th European Hematology Association (EHA) Congress

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Summary

Somatic mutations in the *IDH1* gene are relatively common, occurring in 6–14% of patients with acute myeloid leukaemia (AML), and are especially enhanced in populations such as the elderly.[1-3] Ivosidenib is a first-in-class, oral, targeted inhibitor of the mutant isocitrate dehydrogenase 1 (mIDH1) enzyme. It is approved in the USA for the treatment of AML with a susceptible *IDH1* mutation, as detected by a U.S. Food and Drug Administration (FDA)-approved test in adults with newly diagnosed (ND) AML who are ≥75 years of age or who have comorbidities that preclude the use of intensive induction chemotherapy (IC), and in adults with relapsed or refractory (R/R) AML.[4-6] A recent report from an ongoing Phase Ib study of the ivosidenib plus azacitidine combination, for the treatment of patients with mIDH1 ND AML ineligible for IC, showed a complete remission (CR) plus CR with partial haematologic recovery (CR_h) rate of 70% and demonstrated a favourable safety profile in these difficult-to-treat IC-ineligible patients.[7] AGILE is an ongoing Phase III study of the ivosidenib plus azacitidine combination regimen in adults with mIDH1 ND AML.[8]

Venetoclax is a potent, selective, oral inhibitor of B-cell lymphoma-2. It is approved in the USA in combination with azacitidine, decitabine, or low-dose cytarabine for the treatment of ND AML in adults who are ≥75 years of age or who are IC-ineligible.[9] Azacitidine reduces DNA methylation by inhibiting DNA methyltransferases, and as a monotherapy has shown promising clinical activity in older patients with ND AML.[10] The combination of venetoclax plus azacitidine in treatment-naïve, elderly patients with mIDH1/2 AML showed a CR/CR with incomplete haematologic recovery (CR_i) rate of 71%.[9]

In vitro studies of $mIDH1^{R132H}$ erythroleukaemia cell lines treated with ivosidenib and azacitidine have shown enhanced cell differentiation and potentiation of apoptosis compared to either agent alone.[11]

The authors report a primary analysis of ivosidenib (500 mg daily, Day 15-continuous) combined with venetoclax (Days 1–14 per 28-day cycle), with or without azacitidine (75 mg/m^2, Days 1–7). The dual primary objectives of this Phase Ib/II, open-label, nonrandomised study[12] were to assess the safety and efficacy of ivosidenib in combination with venetoclax, with or without the addition of azacitidine, for the treatment of mIDH1 myeloid malignancies. Eligible patients were enrolled into one of three successive cohorts (Cohort 1: ivosidenib plus venetoclax 400 mg; Cohort 2: ivosidenib plus venetoclax 800 mg; Cohort 3: ivosidenib plus venetoclax 400 mg plus azacitidine). Primary endpoints included safety and tolerability and overall response rate, measured by the International Working Group (IWG) response criteria.[13]

Twenty-one patients (median age: 67; 12 [57%] male) were enrolled. Seventeen patients had AML: nine with R/R AML, five had treatment-naïve AML, and three had hypomethylating agent-failure myelodysplastic syndrome, with progression to secondary AML. Four patients had high-risk myelodysplastic syndrome.

The most frequent (≥15%) Grade 1/2 adverse events (AE) were diarrhoea (75%), nausea (30%), vomiting (25%), and differentiation syndrome (15%). The most frequent (≥15%) Grade 3/4 AE included pneumonia (70%), febrile neutropenia (50%), and abdominal pain (15%). AE of special interest included differentiation syndrome (n=4; Grade >3 in 1) and tumour lysis syndrome (TLS) (n=2), including one Grade 3 TLS event in a $NPM1^+$ co-mutated patient (successfully managed without haemodialysis). No patients died within 60 days of starting treatment, but one death was reported in the study because of febrile neutropenia in the setting of persistent disease. One patient, who had one kidney, had dose-limiting toxicity of TLS. Median cycle lengths for Cycle 1 were 27.0 days, 28.0 days, and 39.5 days for Cohort 1, Cohort 2, and Cohort 3, respectively; and for Cycle 2 were 28.0 days, 29.0 days, and 45.0 days for Cohort 1, Cohort 2, and Cohort 3, respectively.

Response rates are summarised in Table 1. In evaluable patients (n=20), composite CR ([CR_c]: $CR+CR_i+CR_h$) rates were 80% overall (*de novo* AML: 100%; secondary AML/treated-secondary AML: 80%; R/R: 63%), and were 67%, 100%, and 75% by cohort, respectively (median time to best response: 2 months). Fifty percent of patients who achieved CR_c were also minimal residual disease (MRD) negative by flow cytometry. One patient experienced a morphological leukaemia-free state and one patient experienced haematological improvement without CR/CR_i. Of the 20 evaluable patients, six (30%) remained on study, five (25%) proceeded to stem cell transplantation (four in CR and one in a morphological leukaemia-free state), two (10%) were nonresponders, and six (30%) experienced progressive disease after a median of 3 months in CR_c (Figure 1).[14] With a current median follow-up time of 7 months, the median event-free survival was 9.4 months for all patients. Molecular profiling showed a diverse molecular landscape across patients. Active signalling mutations (*NRAS, KRAS, FLT3-ITD/TKD, PTPN11,* and *NF1*) were detected in eight patients (40%). Sixty-six percent of patients without response or with relapse had active signalling mutations and were associated with treatment resistance. The median duration of response in patients with and without active signalling mutations was 1.6 months and 11.9 months, respectively (p=0.043). Median overall survival was 8.5 months in patients with active signalling mutations and was not reached in patients without active signalling mutations (p=0.02).

Table 1: Response rates.

Overall response, N (%)	All cohorts, N (%)	Cohort 1 ivosidenib + venetoclax 400 mg (n=6)‡	Cohort 2 ivosidenib + venetoclax 800 mg (n=6)	Cohort 3 ivosidenib + venetoclax 400 mg + azacitidine (n=8)
Overall response rate	18 (90)	4 (67)	6 (100)	8 (100)
Composite CR*	16 (80)	4 (67)	6 (100)	6 (75)
CR	8 (40)	3 (50)	3 (50)	2 (25)
CR_h	2 (10)	0 (0)	2 (33)	0 (0)
CR_i	6 (30)	1 (17)	1 (17)	4 (50)
Morphological leukaemia-free state	1 (5)	0 (0)	0 (0)	1 (13)
Haematological improvement	1 (5)	0 (0)	0 (0)	1 (13)
Nonresponders	2 (10)	2 (33)	0 (0)	0 (0)
Flow minimal residual disease (negative)†	8 (50)	2 (50)	2 (33)	4 (67)

*CR_h and CR_i represented as mutually exclusive.

†Among patients achieving a composite CR.

‡One patient in Cohort 1 was unevaluable and replaced.

CR: complete remission; CR_h: complete remission with partial haematologic recovery; CR_i: complete remission with incomplete haematologic recovery.

In patients with CR, with a current median follow-up of 2.5 months, duration of response was 3.0 months in MRD-positive patients and was not reached in MRD-negative patients. Median event-free survival was 5.0 months in MRD-positive patients and was not reached in MRD-negative patients; median overall survival was not reached in either group.

Overall, these preliminary data demonstrated that the combination of ivosidenib plus venetoclax with or without the addition of azacitidine was both well tolerated and effective. It was shown that these molecularly targeted combination regimens are effective for advanced mIDH1 myeloid malignancies, with a CR_c in 80% of patients. Undetectable MRD by flow cytometry was found in 50% of patients with CR, with responses currently ongoing. In the triplet combination cohort, undetectable MRD by flow cytometry was found in 67% of patients with CR, with responses currently ongoing. This combination regimen was well tolerated, with a manageable toxicity profile. Treatment cycles longer than 28 days are required with the triplet combination for managing cytopenias. Additional follow-up and accrual in the Phase Ib part of the study is currently ongoing and thus, determination of the recommended Phase II dose and more mature efficacy, tolerability, and biomarker data are forthcoming. In the future Phase II part of the study, the authors aim to confirm efficacy in two cohorts (n=20 each) of treatment-naïve and R/R mIDH1 patients treated with ivosidenib plus venetoclax, with or without the addition of azacitidine.

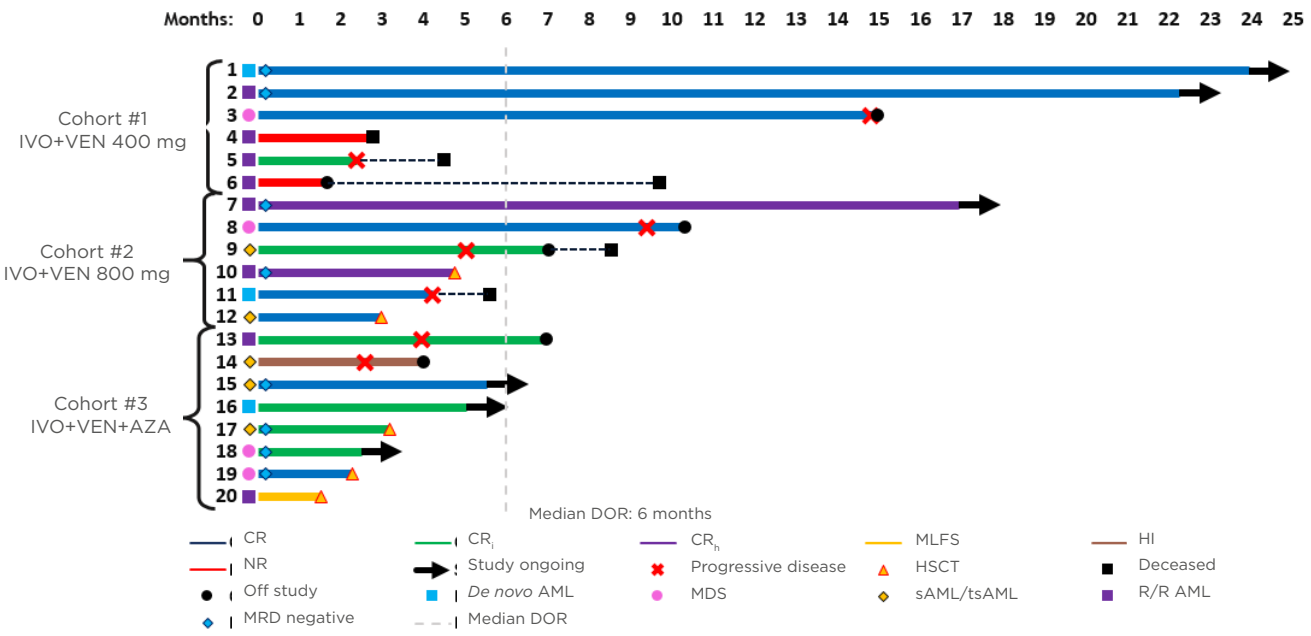

Figure 1: Treatment duration, best overall response, and minimal residual disease.

AML: acute myeloid leukaemia; AZA: azacitidine; CR: complete remission; CR_h: complete remission with partial haematologic recovery; CR_i: complete remission with incomplete haematologic recovery; DOR: duration of response; HI: haematological improvement; HSCT: haematopoietic stem cell transplantation; IVO: ivosidenib; MDS: myelodysplastic syndrome; MLFS: morphological leukaemia-free state; MRD: minimal residual disease; NR: nonresponders; sAML/tsAML: secondary acute myeloid leukaemia/treated-secondary acute myeloid leukaemia; R/R: relapsed or refractory; VEN: venetoclax.

Adapted from DiNardo CD et al.[14]

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Abstract Reviews

The following pages provide summaries of trailblazing abstracts presented at the European Hematology Association (EHA) Virtual Congress (EHA25 Virtual), written by the presenters themselves.

Paused Transcription: A Novel *MIR139*-Silencing Mechanism Downstream of MLL-AF9 in Acute Myeloid Leukaemia

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Keywords: Acute myeloid leukaemia, epigenetic, microRNA, *miR-139*, MLL-AF9, transcriptional regulation.

Citation: EMJ Hematol. 2020;8[1]:54-56. Abstract Review No: AR1.

BACKGROUND AND AIMS

The expression and tight regulation of microRNA is essential for haematopoiesis and the prevention of leukaemia.[1,2] *MIR139*, which is located in intron-1 of the *PDE2A* host gene, is a critical tumour suppressor in human cancers and is commonly inactivated in acute myeloid leukemia (AML).[3,4] However, the mechanism of *MIR139* silencing is still elusive. This study aimed to investigate the effects of *MIR139* reactivation on MLL-AF9 AML, to identify the downstream *miR-139* targets, and to unravel the molecular mechanism behind the silencing of *MIR139* in MLL-AF9 AML (Figure 1).

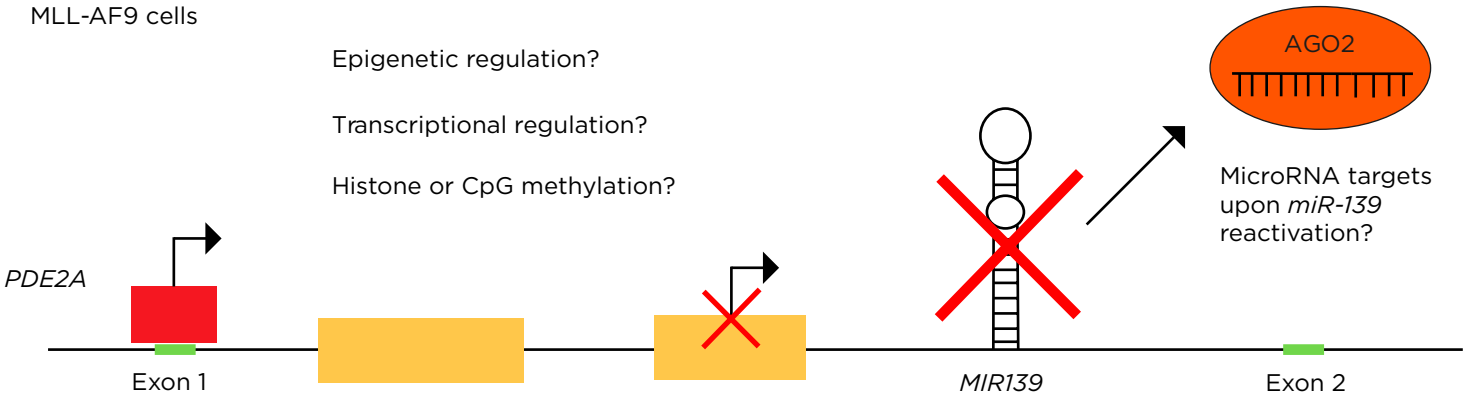

Figure 1: Schematic overview of research questions.

This project aimed to investigate the *MIR139* silencing mechanism in MLL-AF9 AML and to identify the *miR-139* targets that are controlled upon *MIR139* reactivation.

MATERIALS AND METHODS

For this study, the authors selected the AML model with translocation t(9;11)(p22;q23), expressing the mixed-lineage leukaemia *(MLL)-AF9* oncogene, which is an aggressive type of AML characterised by poor prognosis.[5] *miR-139*-inducible lentiviral vectors, next generation sequencing, and proteomics were utilised to determine the tumour-suppressing functions and to identify downstream targets of *miR-139* in MLL-AF9 AML. To investigate the molecular *MIR139* silencing mechanism, the authors employed clustered regularly interspaced short palindromic repeats (CRISPR)-Cas9 sgRNA screens, small-molecule inhibitors, CRISPR-Cas9 knockout mouse models, and performed chromatin immunoprecipitation sequencing (ChIP-seq) data mining, RNA interference, and ChIP-polymerase chain reaction.

RESULTS

The study found that MLL-AF9 expression in haematopoietic stem and progenitor cells caused an 85% reduction of *miR-139* expression. Forced expression of *miR-139* with doxycycline-inducible expression vectors in MLL-AF9 AML caused loss of colony-forming capacity and rapid apoptosis. Next generation sequencing and proteomics revealed *Eif4g2*, a known *miR-139* target, and three novel targets, *Ptprt*, *Map2k6*, and *Hpgd* of *miR-139* in MLL-AF9 AML. The study found that CRISPR-Cas9-mediated knock out of *Ptprt* and *Hpgd* reduced the colony-forming capacity of MLL-AF9 AML, indicating that these targets mediate the tumour-suppressing activity of *miR-139*.

Only *Eif4g2*, *Ptprt*, and *Hpgd* were confirmed as direct targets of *miR-139* by luciferase-based assays in HEK-293T cells, suggesting that the regulation of *Map2k6* is indirectly affected by *miR-139*. The study found that two well-conserved putative enhancer regions, located upstream of *MIR139*, are epigenetically silenced by the polycomb repressive complex 2 (PRC2), demonstrated by SUZ12 occupation, increased H3K27me3, and decreased H3K27Ac levels. PRC2 prefers binding to methylated CpG.[6] Indeed, the study found increased CpG methylation levels in the enhancer regions, compared to the upstream putative promoter. Inhibiting H3K27-specific methyltransferases enhancer of zeste-1 (EZH1) and EZH2, two critical compounds of PRC2, with UNC1999[7] resulted in a large increase of *miR-139* expression and apoptosis of MLL-AF9 AML, but did not change the expression of *Pde2a*. Furthermore, results showed that both individual enhancers were essential for *miR-139* induction, but not for *Pde2a* expression in MLL-AF9 cells treated with UNC1999. In agreement, CRISPR-Cas9-mediated deletion of the individual *MIR139* enhancer regions in mice resulted in strongly reduced *miR-139* levels in normal haematopoietic stem and progenitor cells.

Genome-wide CRISPR-Cas9 sgRNA library screens revealed the transcriptional pausing factor of RNA polymerase II, POLR2M,[8,9] as a novel *MIR139*-silencing factor downstream of PRC2. In agreement, *Polr2m* deletion in *MLL-AF9* AML induced *miR-139* expression and decreased the colony-forming capacity and cell viability. Furthermore, ChIP experiments revealed that POLR2M is located at the transcriptional start site within the most-proximal enhancer region of *MIR139*. This interaction, accompanied by enhanced serine 5 phosphorylation of the C-terminal domain of RNA polymerase II, is indicative of paused transcription.[10]

CONCLUSION

Together, this study indicates that both *miR-139* expression, or inactivation of *miR-139* targets, eliminate MLL-AF9 AML. Furthermore, the study presents evidence for a *POLR2M*-mediated *MIR139*-silencing mechanism downstream of MLL-AF9 and PRC2.

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Gene Therapy For Fanconi Anaemia: A Report on Outcomes in Nine Patients

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Keywords: Bone marrow transplant, cellular therapies, Fanconi anaemia, gene therapy.

Citation: EMJ Hematol. 2020;8[1]:56-58. Abstract Review No: AR2.

BACKGROUND AND AIMS

Fanconi anaemia (FA) is a rare, inherited bone marrow failure syndrome, for which the only available curative treatment is haematopoietic cell transplant (HCT).[1] Gene therapy has been reported to improve bone marrow function in individuals with FA. However, the clinical application of gene therapy is still in its initial stages with controversy over whether gene therapy can potentially replace HCT.[2] This systematic review compares the long-term safety and clinical outcomes of gene therapy versus the standard treatment of choice, i.e., HCT, in FA patients, using the peer-reviewed literature published on this topic.

Table 1: Summary of the clinical trials included.

Variables	Clinical Trial 1	Clinical Trial 2	Clinical Trial 3
Title	Successful engraftment of gene-corrected haematopoietic stem cells in nonconditioned patients with Fanconi anaemia	Stem cell collection and gene transfer in Fanconi anaemia	Gene therapy for Fanconi anaemia in Seattle: clinical experience and next steps
Authors (year of publication)	Rio et al.[3] (2019)	Kelly et al.[4] (2007)	Adair et al.[5] (2016)
Full text available	Yes	Yes	No (Abstract)
Sample size	4	3	2
Mean age	5.9±1.6	13.7±1.6	16.0±8.5
Pre-infusion mean:			
Hb (g/dL)	11.3±0.9	10.7±2.5	NP
Neutrophils (/µL)	1235±472	1423±672	710±56.7
Plts (x10^3/µL)	48.0±21.8	76.0±40.1	61.0±29.7
CD34+ cells (/µL)	118.0±117.0	NP	NP
CFC survival to 10 NM MMC (%)	0	0	NP
Transduced mean:			
CD34+ cells (x10^5/kg)	2.6±1.1	NP	NP
CFC (/kg)	46.0x10^3±76.1x10^3	NP	30.7%
TNC (x10^5/kg)	NP	2.83±2.10	NP
Lentiviral transduction	3x10^8 IU/mL	NP	10 IU/cell
Number of transductions	1	2	1
Vector count number	0.35	NP	1.08
CFC survival after 10 NM MMC (%)	31.0	44.7	NP
Follow-up period	18–30 months	12 months	NP
Blood-cell lines:			
Improvement (numerical/ description)	No	Yes (transient); 6-month follow-up: Hb (g/dL): 13.5±0.7 Plts (x10^3/µL): 90.0±28.3	No
Stabilisation	Yes	Yes	Yes
Genotoxic events	None	None	None

CFC: colony-forming cells; Hb: haemoglobin; MMC: mitomycin C; NM: nonmelanoma; NP: not provided; Plts: platelets; TNC: total nucleated cells.

MATERIALS AND METHODS

This systematic review followed the PRISMA Guidelines. The primary objective was to determine the symptom-free survival rate, serious adverse events, and long-term survival probability of individuals with FA, attributable to gene therapy. Secondary objectives included assessing post-infusion blood cell counts, the use of blood transfusions, or the need for a bone marrow transplant and quality of life post-gene therapy. Randomised controlled trials, prospective clinical trials, retrospective studies, case reports, and case-control studies were included. FA patients, of all ages and gender, irrespective of geographical or healthcare setting, were

considered. Studies (published between 2005 and 2019) focussing on gene therapy with or without standard treatment were included. Table 1 details the studies that were included in the final study.

The authors conducted electronic searches of PubMed, Web of Science, Cochrane Library, and Google Scholar, and screened the reference lists of the included studies to identify potentially relevant studies. The full texts of articles that met the inclusion criteria were reviewed. Reviewers independently extracted data from the included studies using a designed structured data form. The authors assessed the risk of bias using the Cochrane Risk of Bias tool for randomised controlled trials, and also planned to calculate whether statistical heterogeneity was present using the chi-square test for homogeneity, with $p<0.1$ as significant (anticipating a very small sample size). Assessment for publication bias was planned if at least 10 studies were to be included in the final selection.

RESULTS

Three clinical trials were included in the final sample applying strict selection criteria.[3-5] A total of nine patients were therefore included in the study, with a mean age of 10.7±5.7. The mean pre-infusion haemoglobin (g/dl), neutrophils (/µL), and platelets (10^3/µl) were 11.0±1.6 (two studies), 1,181±525, and 61.1±28.7, respectively, and an overall vector count number (VCN) of 0.59±0.60 (two studies). All patients had lentiviral-mediated gene therapy. A 1-year follow-up of most patients showed stabilisation and mild improvement in blood lineages, without any serious genotoxic events. There were no cytogenetic abnormalities reported in patients in two of the studies. A meta-regression analysis could not be conducted due to the absence of randomised trials and limited availability of patient data. Overall, very little long-term follow-up data in any of the patients was observed, thus the study objective of comparing gene therapy to HCT remains inconclusive and unanswered. The authors were also unable to assess quality of life after gene therapy since this was not reported in any study.

CONCLUSION

Gene therapy is an overall safe procedure for FA; however randomised studies need to be conducted to gain a better insight into the beneficial long-term effects it has in patients with FA, and if there is potential to become a standard-of-care treatment.

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Implementation of Haematological Malignancies Patient-Reported Outcome Measure in Clinical Practice: Haematologists' Experience

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Disclosure: The authors have declared no conflicts of interest.

Keywords: Haematological malignancies (HM), haematological malignancies patient-reported outcome (HM-PRO), quality of life (QoL).

Citation: EMJ Hematol. 2020;8[1]:59-61. Abstract Review No: AR3.

BACKGROUND AND AIMS

Patients with haematological malignancies (HM) may experience significantly compromised quality of life (QoL) as a result of the disease and its treatments.[1-4] It is paramount to seek and capture patients' unmet needs in routine clinical practice.[5,6] Until recently, there was no specific patient-reported outcome (PRO) measure for patients with HM to identify symptoms, the impact of the disease and of treatment on patients' QoL in routine haematological practice.[7-8] A new tool, HM-PRO, was developed by the the European Hematology Association Scientific Working Group for 'Quality of Life and Symptoms' (EHA SWG QoL & Symptoms) to measure PRO in individuals with HM in clinical practice.[9-10]

The HM-PRO consists of two scales: Part A (24 items) measuring the 'impact on patients' QoL'; and Part B (18 items) measuring 'signs and symptoms' (S&S) experienced by the patients. Part A had 4 domains: physical behaviour ([PB] 7 items), social wellbeing (3 items), emotional behaviour (11 items), and eating and drinking habits (3 items). Higher scores represented higher impact.

The aim of the study was to determine the value of the HM-PRO in daily clinical practice in Russia and to test its application for evaluating a patient's condition during different stages and states of the disease.

METHODS

Patients aged ≥18 years old with different HM completed the Russian version of the HM-PRO before seeing the haematologist in out- or inpatient settings. Haematologists then reviewed patients' responses during the consultation, as well as completed clinical and demographic information. They also reported on the feasibility of the HM-PRO in clinical practice. Descriptive statistics and parametric and nonparametric tests at a significance level of $p<0.05$ were applied.

Table 1: Haematological malignancies patient-reported outcome medians and interquartile ranges.

Domains	Remission (SD)	Progressive disease	p value
Physical behaviour	14.29 (0.00–35.71)	50.00 (28.57–78.57)	<0.001
Social wellbeing	0.00 (0.00–16.67)	0.00 (0.00–16.67)	0.437
Emotional behaviour	27.27 (13.64–45.45)	31.82 (9.09–45.45)	0.603
Eating and drinking habits	25.00 (0.00–25.00)	12.50 (0.00–50.00)	0.893
Part A total score	18.19 (9.09–31.36)	24.58 (21.02–36.36)	0.060
Signs and symptoms	14.71 (5.88–23.53)	27.94 (14.71–35.29)	0.010

SD: stable disease.

A total of 192 patients and 29 haematologists from five tertiary hospitals in Moscow and St. Petersburg, Russia, were included in a cross-sectional study. Among patients, 93 (48%) were male and the mean age was 50.7 (standard deviation [SD]: ±14.8) years. Distribution according to the diagnoses was as follows: acute myeloid leukaemia (n=43), aggressive non-Hodgkin lymphoma (n=21), chronic lymphocytic leukaemia (n=10), chronic myeloid leukaemia (n=47), Hodgkin lymphoma (n=21), indolent non-Hodgkin lymphoma (n=7), myelodysplastic syndromes (n=14), multiple myeloma (n=22), myeloproliferative neoplasms (n=4), and others (n=3). Out of 192 patients, 58 (30%) patients had stable disease, 120 (63%) were in remission, and 14 (7%) had progressive disease. There were 79 (42%) inpatients and 113 (58%) outpatients. As for physicians, 10 (34.5%) were male, mean age was 36.1 (SD: ±11.4) years, and mean duration of employment was 10.9 (SD: ±10.1) years.

RESULTS

Physicians reported that the HM-PRO was useful for patient management in 155 cases (81%), which included all stages: at diagnosis, during treatment, and at follow-up. In Part A, items from domains PB and emotional behaviour were considered the most useful by haematologists in 38% and 34% of the patients, respectively, in particular: 'difficulty with physical activity/sports' (40%), 'difficulty with work' (28%), 'worrying about treatment' (21%), and 'worrying about future health' (18%). In Part B, the most informative signs and symptoms were 'problems with energy level' (37%), 'tiredness' (32%), 'hair loss' (20%), and 'night sweats' (18%). Physicians reported that the HM-PRO was useful for all patients with progressive disease and for the majority in remission or with stable disease. PB and S&S scores were significantly worse in patients with progressive disease (Table 1).

Impacts on QoL (Part A total score) and S&S (Part B total score) were significantly worse in patients with progressive disease compared to those in remission or with stable disease ($p<0.01$). Patients with progressive disease experienced moderate effects on QoL and S&S whereas those in remission or with stable disease reported small effects on QoL and S&S. Impacts on QoL and S&S were significantly worse for inpatients compared to outpatients ($p=0.003$). QoL impact was significantly worse in patients whose PRO data affected medical decisions compared to those that did not affect medical decisions ($p<0.001$).

CONCLUSION

The authors demonstrated that the newly developed PRO measure for HM is an informative

tool to identify the impact of the disease and its treatment on patients' QoL as well as S&S in this patient population in routine haematological practice. From the haematologists' perspective, the HM-PRO is a valuable tool to capture patients' needs regardless of the stage and state of the disease. The use of HM-PRO in clinical practice may facilitate the discussion between patients with HM and clinicians on an individual basis to better deliver patient-centred care.

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Integrative Analysis of the Genomic Landscape of Hodgkin Lymphoma Using Liquid Biopsies

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INTRODUCTION

The genomic landscape of Hodgkin lymphoma (HL) is not well understood because of the scarcity of Hodgkin-Reed–Sternberg cells, which makes conventional genotyping difficult. Liquid biopsies have shown to be a feasible tool to unravel the genomic landscape of HL because Hodgkin-Reed–Sternberg cells release substantial amounts of circulating tumour DNA (ctDNA) into the blood.[1-3]

Although current treatment outcomes with staging, risk-factor-based, and/or PET-stratified treatment are excellent, interim PET is far from perfect and patients are often over-treated.[4-5] Hence, the aim of this study was to understand the genomic landscape of HL using whole exome sequencing (WES) of liquid biopsies. With this approach, biological upfront risk stratification to ultimately individualise patient treatment, while also minimising side effects, was investigated.

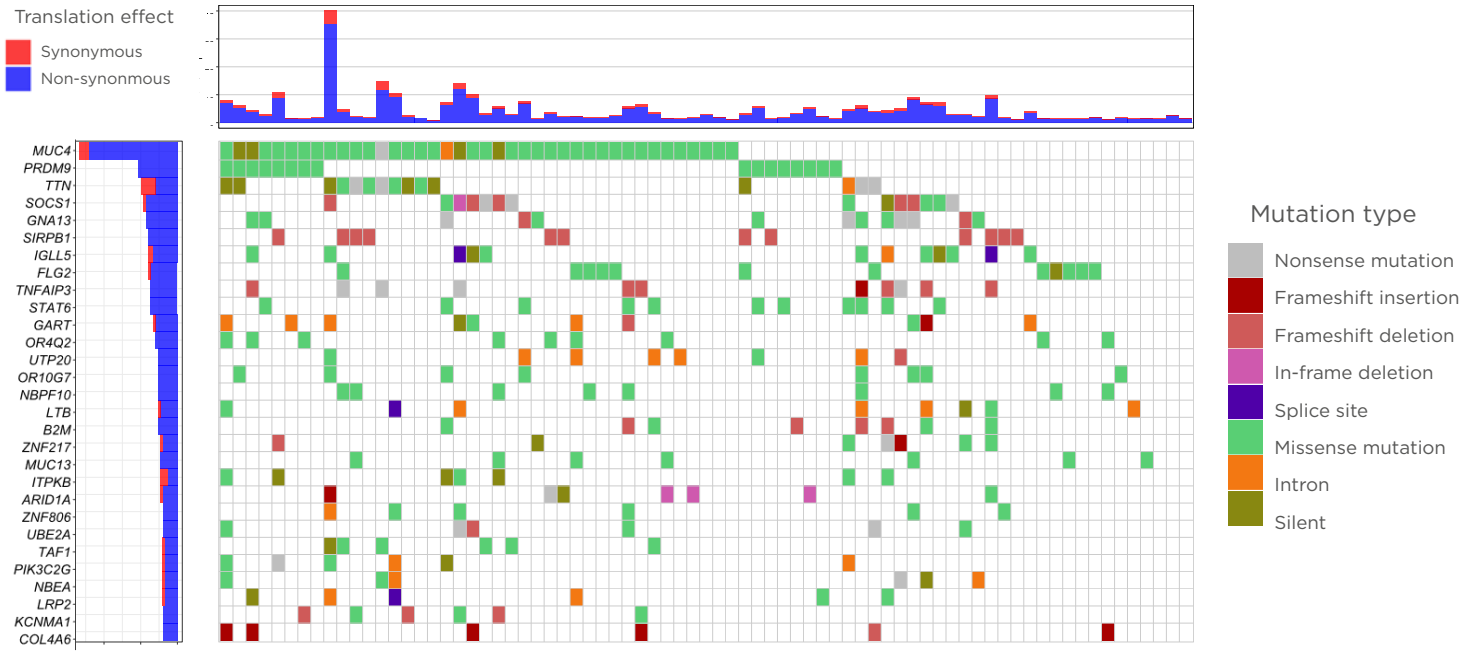

Figure 1: The genomic landscape in Hodgkin lymphoma.

Only significant tumour suppressor genes or oncogenes included (20/20 rule by Vogelstein et al.).[6]

METHODS

75 unselected, newly diagnosed, advanced-stage HL patients were included. All samples underwent pre-analytical processing, extraction of the ctDNA, and matching germline controls and high-depth WES (targeting 37 Mb of the human genome). An in-house customised pipeline was used for two-fold error reduction using unique molecular identifiers and digital error suppression. As part of the validation, results were compared to deep targeted sequencing (>2,000x coverage) and a per-patient concordance of 75% (95% confidence interval: 65%–86%) was found. Furthermore, allele frequencies by WES were highly correlated with the allele frequencies of targeted deep sequencing of ctDNA (r=0.8664; p<0.00001).

RESULTS

Several already known but also novel, recurrently mutated tumour-suppressor or oncogenes were identified. Frequent occurrence of previously described alterations in *SOCS1*, *GNA13*, *IGLL5*, *TNFAIP3*, and *STAT6* were confirmed. In addition, novel recurrently mutated loci were identified in *PRDM9*, *SIRPB1*, and *FLG2* (Figure 1).

Analysing significant copy number variations, recurrent deletions with peaks at *1p36.13* (*SPEN*), *6q23.3* (*TNFAIP3*), *14q13.2* (*NFKBIA*), *21q22.12* (*RUNX1*), and amplifications with peaks at *4q24* (*NFKB1*), *5p15,33* (*TERT*), *7q36.1* (*MLL3*), and *9p24.1* (*PD-L1*) were found.

When investigating COSMIC single-base substitution signatures (SBS), the most commonly identified was SBS1 (ageing), followed by SBS3 (failure of double-strand repair) and SBS9 (noncanonical AID). Interestingly, SBS25 (HL cell-line specific), previously only identified in HL cell-lines, was described in a patient cohort for the first time.

Several novel relationships within the genomic landscape of HL were identified and a subgroup with higher mutational burden associated with either mutations in *B2M* (p=0.0181) or high-level amplification of the *PD-L1* locus (p=0.0031) was discovered. One might speculate that this subgroup of highly mutated HL relies on multiple immune-escape mechanisms.

By using non-negative matrix factorisation, two clusters of patients that shared similar genomic characteristics with distinct mutational drivers and clinical features were identified. Cluster 1 patients had higher Eastern Cooperative Oncology Group (ECOG) grades, whereas Cluster 2 patients had a higher proportion of nodular sclerosis, extra-nodal disease, and higher mutational burden.

Finally, a preliminary, biological risk stratification model based on high- and low-risk genetic alterations was created. A good outcome was defined as PET2-negativity, whereas PET-2-positivity was defined as a bad outcome. It was possible to distinguish three risk groups with the model. In the low-risk group, 8% of patients were PET-2-positive; this was 30% in the intermediate-risk group and 72% in the high-risk group.

CONCLUSION

In summary, this study is one of the most comprehensive studies looking at the genomic drivers of HL with a novel liquid biopsy approach.

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Mechanistic Insights into the Inhibition of Regulatory T Cells by Dasatinib in Chronic Myeloid Leukaemia Patients with Clonal Lymphocytosis

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Keywords: Chronic myeloid leukaemia, clonality, dasatinib, regulatory T cell (Treg).

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BACKGROUND AND AIMS

Dasatinib is a potent inhibitor of lymphocyte-specific protein tyrosine kinase (Lck), which plays a pivotal role in T-cell receptor (TCR) signalling, with immediate downstream targets including ZAP70 and linker of activated T cells (LAT), which are also implicated in regulatory T cell (Treg) development. Signal transducer and activator of transcription 5 (STAT5), the downstream target of IL-2, also plays a critical role in Treg differentiation and maintenance of FOXP3 expression through its binding of the promoter region of the *FOXP3* gene. A subset of patients on dasatinib develop clonal large granular lymphocytosis (LGL) which is associated with immune-mediated toxicity and improved outcome.[1,2] The authors hypothesised that a reduction in Treg frequency and function would correlate with the expansion of clonal LGL populations in patients receiving dasatinib.

METHODS

Phosphoflow cytometry was performed in Tregs and T effectors to assess the effect of dasatinib on TCR signalling.[3] Cells were activated with the phosphatase inhibitor H2O2 and were analysed for phosphorylation of ZAP70, LAT, and STAT5. A gating strategy of CD4+/CD25+/FOXP3+/CD127lo cells was used for identification of Tregs, with $FOXP3^{hi}/CD45RA^{-ve}$ cells denoting effector Tregs. Intracellular flow cytometry was also performed on T effectors after stimulation with OKT3, assessing the impact of dasatinib on cytokine expression, including TNFα, interferon-γ, IL-2, -4, and -10.[4]

RESULTS

Fifteen patients with chronic myeloid leukaemia (dasatinib [n=11], imatinib/nilotinib [n=4]) and five healthy controls were recruited. Patients on dasatinib had lower Tregs compared with the non-dasatinib group (mean CD3+ cells: 1.3% versus 2.0%; mean CD4+ cells: 2.6% versus 4.3%; p=0.01 and p=0.007, respectively). Dasatinib-treated patients also had a lower percentage of effector Tregs: 11.5% versus 22.1% (p=0.0097) (Figure 1A).

Patients on dasatinib had significantly reduced phosphorylation of ZAP70, LAT, and STAT5 compared with the non-dasatinib group, in CD4+ cells, CD8+ cells, and Tregs, following stimulation (phosphorylated STAT5 mean increase in median fluorescence intensity [MFI] of 4.1 versus 21.7 in CD4+ cells; 6.1 versus 28.2 in CD8+ cells; and 4.4 versus 22.6 in Treg [p=0.0001, p=0.0001, and p=0.001, respectively]) (Figure 1B).

Mean absolute increase in IL-2 expression was also lower in patients on dasatinib (0.9 versus 7.0 in CD4+ cells; 0.3 versus 3.0 in CD8+ cells; p=0.001 and p=0.014, respectively). Five patients on dasatinib had reversal of CD4:CD8 ratio and lymphocytosis, in line with clonal LGL populations, with TCR clonality confirmed by PCR. These patients had lower Tregs compared with other patients on dasatinib, with a mean CD3+ cells percentage of 0.9% versus 1.8% (p=0.035). A lower increase in MFI within isolated Tregs following stimulation was seen in this group, when compared with patients on dasatinib with normal CD4:CD8 (phosphorylated ZAP70: 1.8 versus 0.8, p=0.024; phosphorylated LAT: 4.4 versus 1.4, p=0.05; phosphorylated STAT5: 7.4 versus 2.0, p=0.15) (Figure 1C).

CONCLUSION

Dasatinib potently inhibits signalling from the TCR in T effectors but also in Tregs, as indicated by inhibition of phosphorylation of ZAP70 and LAT, as well as STAT5, which is essential for transcription of FOXP3. Dasatinib-treated patients have a reduction in proinflammatory cytokine expression within T effectors, with the most significant inhibitory effect seen against IL-2. Tregs have abundant expression of the IL-2 receptor on the cell surface and binding leads to STAT5 signalling.

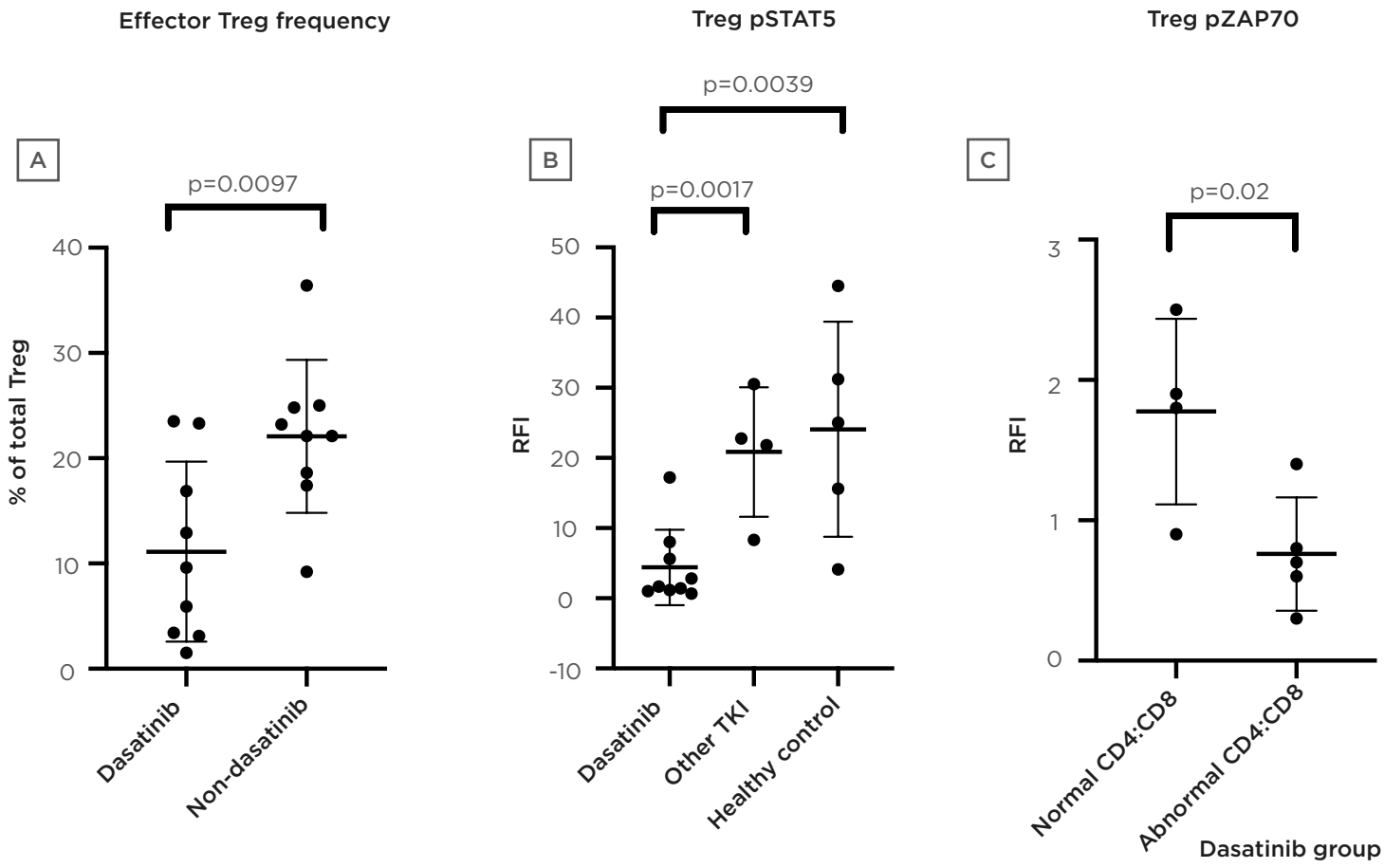

Figure 1: Effects of dasatinib on regulatory T cells.

A) Proportion of effector regulatory T cells (Tregs) in the dasatinib group compared with the non-dasatinib group. **B)** RFI of pSTAT5 in Tregs in the dasatinib group, other TKI group, and healthy controls. **C)** RFI of ZAP70 in Tregs in dasatinib patients with CD8+ lymphocytosis compared with the dasatinib group with normal CD4:CD8.

pSTAT5: phosphorylated signal transducer and activator of transcription 5; RFI: relative fluorescence intensity; TKI: tyrosine kinase inhibitor; Treg: regulatory T cell.

A subset of patients on dasatinib with clonal LGL populations have further reduction in frequency and function of Tregs as assessed by signalling from the TCR and IL-2 receptor. These findings may explain the mechanism of lymphocytosis in this group and could be used to predict improved outcomes with dasatinib.

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Identification of HIF2α as a Novel Determinant of Acute Myeloid Leukaemia Block of Differentiation Poses its Inhibition as a Potential Therapeutic Opportunity for Acute Myeloid Leukaemia Patients

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Keywords: Acute myeloid leukaemia (AML), all-trans retinoic acid (ATRA), differentiation therapy, hypoxia inducible factors (HIF)2α, PT2385.

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Signalling via hypoxia inducible factors (HIF)1α and HIF2α is importantly implicated in cancer,[1] although it has been predominantly studied in solid tumours. In leukaemia, particularly in acute myeloid leukaemia (AML), contrasting evidence suggests that HIF factors may act as oncogenic drivers or tumour suppressors depending on the leukaemic subtype, or in pre-leukaemic phase versus fully developed leukaemia.[2]

AML is a complex and heterogeneous disorder characterised by a variety of genetic and epigenetic alterations that cause uncontrolled cell proliferation, halt apoptosis, and arrest differentiation at different stages of myeloid committment.[3] AML treatment has long been based on intensive chemotherapy, with the recent addition of haematopoietic cell transplantation for high-risk patients, and newly approved targeted therapies for leukaemia subtypes with specific mutations.[4] Current AML therapy causes high remission rates, but relapse occurs frequently and 5-year overall survival is still discouragingly low, leading to an urgent need of new therapeutic options. Important exceptions are patients with acute promyelocytic leukaemia (APL), who are exquisitely responsive to the differentiation agent all-trans retinoic acid (ATRA). The incredible success of ATRA in treating APL provided a rationale for using ATRA-based therapies for other AML subtypes;[5] however, most non-APL AML are resistant to ATRA-induced differentiation due to closed chromatin conformation and epigenetic silencing at differentiation genes.[6]

Within this framework, the authors found that HIF2α plays an unprecedented function in AML, by taking part in the myeloid differentiation block that characterises this disease.

To identify specific functions of HIF1α and HIF2α in different AML subtypes, their expression was reduced via shRNA-mediated silencing in 5 AML cell lines representative of diverse morphological and genetic AML. HIF1α and HIF2α played important oncogenic functions in all AML cell lines tested, via increasing cell proliferation and clonogenic capability. However, specific silencing of HIF2α and not HIF1α was sufficient to trigger differentiation of AML blasts. To identify HIF-specific gene regulation and obtain molecular insights into this newly identified function of HIF2α, RNA sequencing was performed in two AML cell lines upon HIF1α or HIF2α suppression. Results showed that HIF1α predominantly regulates metabolic pathways, while HIF2α promotes the expression

of genes governing cell fate determination, differentiation and cancer via heterochromatin formation and chromatin-remodeling events. In parallel, when HIF2α is expressed, entire gene signatures linked to myeloid differentiation are transcriptionally suppressed.

To test the relevance of these findings for AML therapy, the outcome of HIF2α inhibition was evaluated on three AML patient-derived xenograft models by using the non-selective HIF inhibitor EZN-2208.[7] Additionally, *in vitro* responses were measured to a new small molecule inhibitor of HIF2α, PT2385, which is currently being tested in clinical trials for patients with kidney cancer and glioblastoma[8].

Results showed that HIF2α targeting reduces leukaemia progression by impacting cell proliferation and triggering myeloid differentiation, although the extent of leukaemia debulking and differentiation varies in different AML. Importantly, HIF2α inhibition cooperates with ATRA in promoting AML differentiation via positive regulation and reinforced expression of genes involved in myeloid maturation and activation.

In conclusion, HIF2α is part of the differentiation block that characterises AML blasts, and its inhibition may represent a valuable therapeutic opportunity to promote AML cell maturation and exhaustion. In addition, HIF2α inhibition may co-operate with other differentiation agents, including ATRA, to optimise current treatments and offer more effective combinatorial therapeutic strategies.

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Comparison of Decitabine with Venetoclax versus Intensive Chemotherapy Using Propensity Score Matching and Treatment-related Mortality Risk Scoring

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BACKGROUND AND AIMS

Acute myeloid leukaemia (AML) usually presents in older patients over the age of 65 years.[1] A large proportion of such patients are frail or have comorbidities that make them poor candidates for intensive therapies.[2] Venetoclax-based lower-intensity regimens are now established as standard therapy for older or unfit patients with AML.[3,4] However, initial clinical trials of venetoclax did not incorporate objective methods for delineating patients who are considered 'unfit' for intensive chemotherapy. Consequently, the benefit of venetoclax-based regimens in truly unfit patients has been debated, and experts have advocated for randomised controlled trials against intensive chemotherapy.[5]

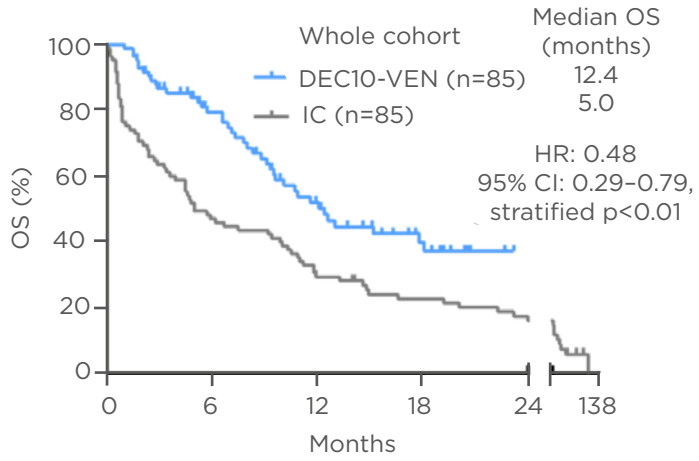

Figure 1: Overall survival in patients with newly diagnosed acute myeloid leukaemia treated with DEC10-VEN, and a propensity score-matched cohort of patients treated with intensive chemotherapy.

CI: confidence interval; DEC10-VEN: 10-day decitabine with venetoclax; HR: hazard ratio; IC: intensive chemotherapy; OS: overall survival.

The authors conducted a retrospective study to address these questions.[6]

MATERIALS AND METHODS

The authors compared outcomes of 85 patients with newly diagnosed AML, treated on a prospective Phase II trial of 10-day decitabine and venetoclax (DEC10-VEN), with a historical cohort of patients treated with intensive chemotherapy containing cytarabine of at least 1 g/m^2/day.[7] The historical cohort of 85 patients was selected from over 1,300 patients using propensity score matching. To better understand outcomes in patients deemed unfit by objective methods, the authors used a previously validated treatment-related mortality scoring that classified patients at low versus high risk of 30-day mortality from intensive chemotherapy.[8]

RESULTS

The two cohorts of patients treated with DEC10-VEN and intensive chemotherapy were well balanced in terms of baseline characteristics. More than 50% of patients were >70 years, >30% patients had Eastern Cooperative Oncology Group (ECOG) performance status scores of 2 or higher, nearly 30% patients were at high risk of early mortality form intensive chemotherapy, and nearly two-thirds of patients had European LeukemiaNet (ELN) adverse risk disease. The authors found that DEC10-VEN led to significantly higher rates of complete remission compared to intensive chemotherapy (62% versus 42%; p=0.01), lower rates of relapse (34% versus 56%; p=0.01), lower 30-day mortality (1% versus 24%; p<0.01), and longer overall survival (OS) at 12.4 months versus 5.0 months (Figure 1). Patients at both low risk as well as high risk of early mortality from intensive chemotherapy derived benefit with DEC10-VEN and had significantly longer OS.[6] Subgroup analysis for OS showed benefit with DEC10-VEN over intensive therapy in most subgroups and multivariable analysis confirmed improved outcomes with DEC10-VEN over intensive therapy for most outcomes including complete remission rates, early mortality, and OS.

CONCLUSION

The authors concluded that in this retrospective analysis, DEC10-VEN showed better outcomes compared to intensive chemotherapy in newly diagnosed AML. Patients who were at both low risk as well as high risk of early mortality with intensive chemotherapy appeared to benefit from DEC10-VEN. These results have implications for the design of future clinical trials incorporating venetoclax-based regimens. The authors

commented that clinical trials evaluating the role of venetoclax with hypomethylating agents in younger and older 'fit' patients are currently ongoing at their institution.

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Congress Interviews

In the following pages you will find our captivating interviews with the EHA Chair of the European Board for Accreditation in Hematology, EHA Chair Curriculum Committee, EHA Chair Guidelines Committee, and a panel interview with two aspiring haematologists from the YoungEHA Committee.

Prof Margarita Guevova

EHA Chair of European Board for Accreditation in Hematology
National Specialised Hospital for Active Treatment of Haematological Diseases, Sofia, Bulgaria

Q1 You received your medical training at the Medical University of Sofia and PhD at the National Center of Hematology in 2000. What, in your opinion, are the most significant advances in haematology since this time?

These were times of innovation and change of paradigms. This refers to the outburst of novel diagnostic tests and treatments but also to a real shift of practices and processes that brought together different and new ideas in a way that significantly impacts our profession. By exciting technological innovation in research and diagnostic approaches we were able to unravel complex biological processes underlying diseases of the blood and blood-forming organs and identify many key biomarkers that allowed us to recognise entities with a distinct picture and biology and specific response options. Large-scale studies of the genome, gene expression, epigenetics, cell-to-cell interactions, and immunity changed our concepts and approaches. This came together with the development of several new molecules and targeted drugs that could more effectively treat diseases. Today, diseases that were inevitably fatal when I started my career can be successfully controlled and even cured. Furthermore, the patients may reach a life expectancy comparable to that of the general population. Unlocking and mobilising the huge potential of cells against diseases gave us powerful strategies (from transplantation to

"Scientific journals remain one of the major portals for gaining new information"

new CAR T-cell therapies). However, information and communication are the other avenues of innovation that made all this possible. Bioinformatics is an unimaginable tool for effective data analysis and novel applications; however, transfer of information and communications has allowed us to take big steps in professional community awareness, cooperation, and collaboration. Last but not least, for me personally the shift from expert-centred haematology towards an integrated multidisciplinary approach is an exciting and expiring professional environment which will be to the benefit of our patients.

Q2 By what means do you stay up to date with the latest cutting-edge advancements in haematology?

I am happy to live in times that provide us with multiple information channels. Scientific journals remain one of the major portals for gaining new information; however, nowadays with online access and means to select articles on particular topics it is amazing how you can get a comprehensive in-depth view in a short time. I have subscribed to several online channels for haematology updates as well. In addition, coming from eastern Europe I am happy to live during times when the world became more accessible to us in various aspects. Personal contact with colleagues from all over the world allowed me not only to be aware of the advances made but to comment on specific issues and to find the best ways to implement them in our practice as well. Attending meetings and conferences is a way to expose me to the latest breakthroughs and gives me opportunities for interaction. Unfortunately, the COVID-19 pandemic showed us how vulnerable we are and in one go took away these valuable personal contacts. Yet living in modern times, our communication did not stop and we saw the power of new information channels including webcasts, video conferences, and plenty of publications that keep us informed and connected. Now we can also appreciate the advantages of online training where the latest advancements can be so rapidly incorporated and accessible to anyone, no matter the location.

Q3 You were editor for a recently published ebook titled 'Hematology: latest research and clinical advances.' What approach do you take towards ensuring the highest possible quality in the educational materials you collaborate on?

Together with my colleague Prof Gueorgui Balatzenko, we edited a couple of haematology books, including 'Hematology: latest research and clinical advances.' Each chapter was a separate publication that reflected views and concepts of authors coming from different countries and professional backgrounds. The challenge was to integrate them in a useful book with examples of novel insights in our current understanding of the biology and clinical presentation, risk assessment, and therapeutic challenges in specific haematological diseases. We put in a lot of effort to develop a clear and easy to read text. Our goal was that each chapter contributed with a comprehensive and concise update in the rapidly evolving field and the content was relevant and interesting for specialists involved in the clinical management and experimental research in haematological diseases. As expected, malignancies were well covered; however, benign aspects of haematology were also present in this book with some hot topics such as the new therapies improving the outlook of bleeding and clotting disorders, as well as sickle cell disease, which 1 year later became one of the topics-in-focus of EHA. Major principles we followed in the editorial process were relevance, lack of bias, and integrity.

Q4 What do you believe are the biggest challenges currently facing the haematological research community?

The recent scientific breakthroughs have been amazing and created unprecedented advances in haematology. Yet, there are even more challenges for the conduct of medical research than ever. Some refer to scientific problems that must be solved. For example, from recognition and control of diseases we moved to prediction and cure in a substantial number of disorders. However, there is still no way to recognise individuals at risk and prevent the development of haematological malignancies. Hopefully, we are on the verge of the next paradigm shift (from 'reactive' to 'preventive'). New studies aiming at preventive strategies are extremely important to pave the future of effective prevention prior to successful therapy. Big data platforms are continuously identifying new and increasing numbers of potential therapeutic targets and many novel molecules are in the pipeline. However, the time for finding a new level of synergising these technologies has come and conceptually new models for conducting clinical trials are needed, where margins between disciplines will blur. Computational biology and science, mathematics, physics, and engineering are gaining prevalence in the field. More than ever, collaboration and a multidisciplinary approach are the key for success.

However, there are other categories of challenges that may be far more difficult to overcome. There is a general concern about the increasing gap between the escalating costs of research and the access of academic institutions to funding sources that will allow them to conduct independent studies and prevent inappropriate financial influences. Centralisation and increasing bureaucracy constrain scientists' creativity. Inequalities in access to research funds or networks, both between countries and between institutions, can lead to a disregard for the diversity of ideas needed for progress. Given the increasing pace of scientific development and the lack of a sufficient number of physicians and scientists can also be a limiting factor in ensuring that science becomes a reality and innovation is put into practice, contributing to the transformation and improvement of people's lives.

Scientific integrity, independence of research, equality, high ethical standards, and ongoing professional development should remain the norm and enlighten the future of haematology science.

Q5 On top of your duties with the EHA, you have held roles within the Bulgarian Society of Hematology. Has advocating haematological excellence in your home region always been a passion of yours?

The Bulgarian Society of Hematology has been the home of my efforts for many years, including my early haematology career. For two terms (2011–2019) I was President and these were years devoted to the major goals defined by the Board: excellence and increased prestige of haematology. We accomplished important achievements during this period that I am very happy about. The society developed a medical standard in haematology approved by the Ministry of Health as well as the regularly updated national guidelines for diagnosis, prevention, and treatment of haematological diseases. Our

activities contributed to the enhancement of the role and the importance of the discipline and further improved the dialogue and relationships with health authorities in order to achieve higher levels of medical care for patients with blood diseases. A major objective of the society is to unite and assist our members working in the field of haematology and to create conditions for their professional development. In particular, we assist young residents and specialists by providing training and continuous education. We were successful in establishing working groups (chronic lymphocytic leukaemia and lymphoma, plasma cell disorders, myeloproliferative neoplasms and myelodysplastic syndromes, anaemia, and haemorrhagic disorders, haematopoietic stem cell transplantation, Gaucher's disease, and laboratory diagnosis) that developed guidelines and conducted nationwide studies on the epidemiology and major clinical and laboratory features of haematological entities. We have placed the young generation in the focus for the last years. We tailored our activities using surveys amongst young haematologists to investigate their attitudes. I am proud that a national symposium for trainees and young specialists has been set as a regular yearly activity that provides both education and a platform for their own presentations. Finally, a significant effort has been put to strengthen the relationships with the family of European haematology societies and the EHA. Now, the new board of the society can rely on the previous experience and receive all my support.

Q6 You are the current Chair of the EHA European Board for Accreditation in Hematology (EBAH), a position that rotates every 2 years; what element of the role do you enjoy the most?

I value the interaction with haematologists coming from different countries and various haematological fields united by the common understanding of quality, value, integrity, and dedication in continuous education of medical specialists. I enjoy the discussions and debates, the brain storming, and the chaos followed by the sudden well-defined solutions. Furthermore, I like the ease of becoming friends.

Q7 Please elucidate to our readers the primary goals that the Board is currently working towards. How will these goals be achieved?

The mission of EBAH is to stimulate and support harmonised high-quality continuous medical education in haematology, both for individuals and organisations, in order to provide the highest possible standard of patient and public healthcare within Europe. Continuing medical education/continuing professional development (CME-CPD) is widely accepted to encourage individual practitioners to maintain and develop professional knowledge and skills to keep up to date with latest developments within the field. When spending valuable time on training activities, it is essential to ensure that one is attending a high-quality educational programme. EBAH has been established as an independent accreditation body in response to this need. Our plan at present comprises several main goals: 1) to develop and implement standards and guidelines for CME-CPD activities; 2) to receive legitimacy and quality assurance through external review and mutual agreement with other accreditation bodies; 3) to gain further awareness and recognition through national and international authorities and haematology organisations; 4) to foster interactions and collaborations in CME-CPD accreditation practice and; 5) to provide accreditation for unbiased and transparent education in haematology after strict reviewing and to consider the highest quality standards and maintain a CME users platform.

I am pleased to announce that last month we uploaded a brand new 'EBAH standards and guidelines for CME-CPD activity accreditation' as well as 'EBAH standards and guidelines for CME-CPD provider accreditation" on our website.[1] Education organisers can find useful recommendations that will allow them to improve and receive accreditation. In addition, EBAH may award accreditation to highly reputable scientific and medical associations and societies as education providers after strict reviewing and monitoring if they consistently show that they follow the standards and meet the requirements for delivering independent CME-CPD that accelerates learning, change, and improvement in healthcare. We see EBAH accreditation as an important quality stamp for activities that benefit and develop haematology and related fields.

In terms of awareness and recognition, EBAH relies on the representation of the major international organisations in the field of haematology in the board composition: EHA, International Society of Transfusion Medicine (ISTM), International Society on Thrombosis and Haemostasis (ISTH), European Society for Bone Marrow Transplantation (EBMT), and the EBMT Nurses Group. Further interaction with national European haematology societies is foreseen.

Q8 What are some of the biggest challenges towards effective accreditation in the European haematology field, and how is the Board meeting these challenges?

There are several levels of challenges for accreditation of CME-CPD programmes regardless of the medical specialty. A major problem is that there are no specific legal or legislative mandates for CME-CPD accreditation on the European international level. CME-CPD accreditation has emerged as another example of professional self-regulation. However, the lack of clarity or pan-European regulations challenges the implementation of international principles and rules that would be recognised by both European accreditors and national regulators and would serve the individual physicians. In an attempt to find solutions, we are active in communication with other accreditation bodies in Europe and worldwide. EBAH is one of the founders of Continuing Medical Education-European Accreditors (CME-EA), a non-profit association that has devoted its mission to promote harmonisation of CME-CPD accreditation as part of a quality assurance process aiming to improve physicians' performance and patient outcomes. We agreed that fragmentation should not be the European answer to providers and learners in CME-CPD. Together we work through dialogue and consensus to set common standards and to explore means to get broad acceptance at the national level.

EBAH aims to be the reference accreditation board in Europe for unbiased and transparent CME in haematology. This means that all elements of the programme, development, design, and execution are free of any control of commercial interest and/or any other undesirable influence. However, there have been attempts by industry to be accepted by accrediting bodies as a direct provider of accredited CME-CPD. Such a move would open the door to the introduction of an inevitable bias in CME-CPD using framed information in life-long learning. In this regard EBAH sees its role in giving clear and transparent definitions, rigorous application of appropriate principles and rules, and being in a position to enforce its own standards. In addition, our categorical position has been featured in a set of publications and position papers authored by EBAH and collaborators from CME-EA and other European medical societies and accreditation boards.

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"New studies aiming at preventive strategies are extremely important to pave the future of effective prevention prior to successful therapy"

Prof Antonio Almeida

European Hematology Association (EHA) Chair of the Curriculum Committee
Head of Haematology, Hospital da Luz Lisboa, Lisbon, Portugal

Q1 You have worked in haematology now for 20 years, completing your specialty training in 2002. Why haematology? What drew you to the field, and continues to hold your interest 20 years later?

My interest in haematology arose by serendipity: it was one of the house jobs during my junior residency rotations at St George's Hospital in London, UK. At that time, I was attracted by the variety of pathologies and treatments but above all by the proximity achieved with the patients who were admitted for long periods of time.

As I dove deeper into the speciality I became increasingly drawn in by the close links between clinical practice and laboratory diagnosis: the totally new world which morphology opened up for me and the possibility of investigating diseases myself using multiple laboratory techniques. No less fascinating was the closeness between translational research and clinical practice. I was fortunate to work at St Bartholomew's Hospital, London, UK whilst the first rituximab trials were being conducted and at the Hammersmith Hospital, London, UK whilst the seminal imatinib trial was underway. Not only did these trials produce the huge enthusiasm that novel treatments generate but they were even more interesting because of the understanding of the underlying mechanisms by which these treatment options worked.

Twenty years later these are still the features that fascinate me in haematology: the enormous variety of diseases, from inherited to acquired, benign to malignant, acute and chronic; the closeness to the diagnostic laboratory and the use of morphology as part of the patient's physical examination; and the closeness of translational research to clinical practice, with novel treatment modalities appearing almost immediately after the discovery of a pathophysiological mechanism.

Q2 Having undertaken your medical training in the UK (medical school at Cambridge University, specialty training in haematology, clinical research fellowship at Imperial College, London), you now head the haematology department at Hospital da Luz, Lisbon, Portugal. In your experience, have there been differences in working in haematology between the UK and Portugal?

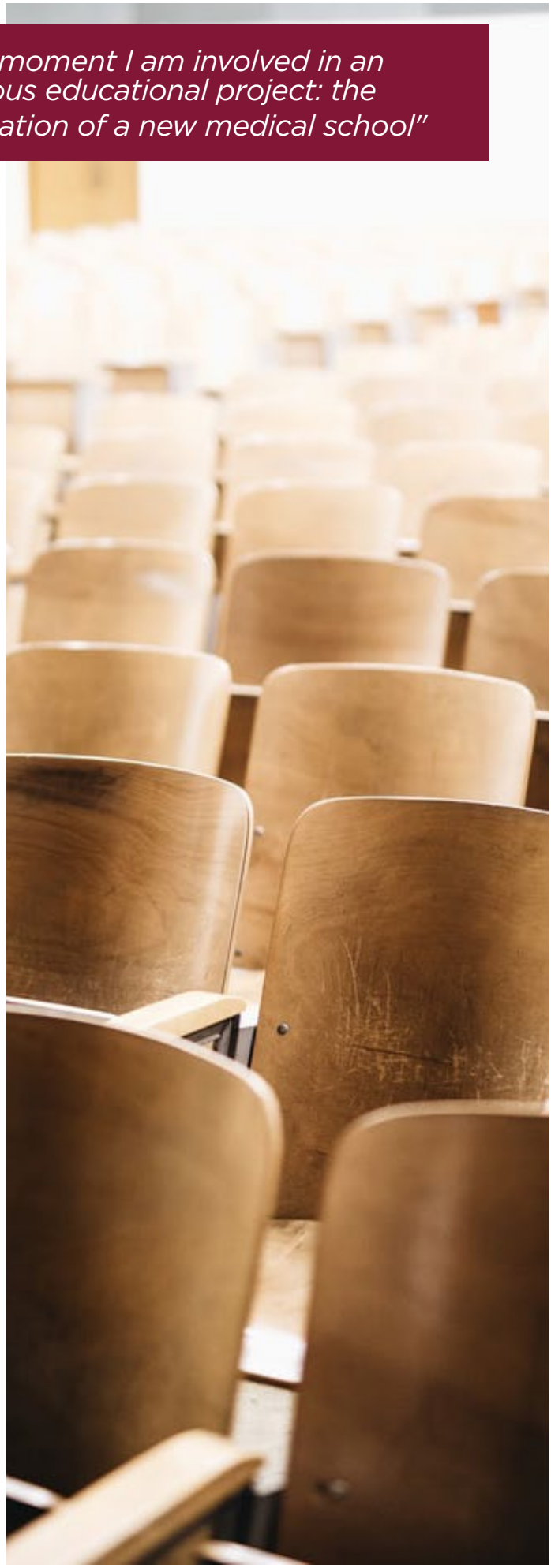
Contrary to what many friends and family warned me, moving from the UK to Portugal was by no means a shock. I was very fortunate to have had Dr Antonio Parreira as Head of Department in Lisbon. He stimulated my interests, career progression, and international contacts, especially with the EHA. He had the same mentor attitude as I had experienced in the UK with Prof John Goldman, Prof Irene Roberts, and many others and this certainly made the transition easier.

Changing institutions is a very enriching experience. It promotes mental flexibility and teaches us to work in different ways to achieve the same objective. Having said this, the experience of changing countries has been a strong incentive to promote the harmonisation of haematology education in Europe. I have realised how different the practices can be between countries and even between institutions within the same country. I feel it is very important to bring the full richness of haematology to everyone who works in this field.

"Changing institutions is a very enriching experience. It promotes mental flexibility and teaches us to work in different ways to achieve the same objective"

Q3 You have a very strong background in academia, completing both a PhD and a clinical research fellowship. How great an impact has your research background had on your clinical practice?

"At the moment I am involved in an ambitious educational project: the implementation of a new medical school"



My PhD project involved the biochemical and molecular characterisations of a very rare disease, inherited glucose phosphate isomerase (GPI) deficiency, and, subsequently, a therapeutic strategy to treat these patients. This project was very broad in its approaches, spanning clinical haematology and basic science, and the results were extremely gratifying.

Research had an enormous impact on my career and my clinical practice. Firstly, it taught me how to think about and approach scientific problems. Secondly, it has brought me into contact with disease mechanisms and with specific techniques to investigate and dissect these mechanisms. Overall, it really made me look at diseases in a different way. I started to look more deeply into the pathophysiology of diseases to understand how these provoked the various disease manifestations and tried to devise strategies by which these could be tackled.

Q4 You have research interests in the role of epigenetics in haematological diseases, and lead a Haematology Epigenetic research group. This is a fairly new area of focus in haematological research, what impact do you hope for it to have on future treatment?

My research group looks into the impact that histone acetylation may have on the pathophysiology of myeloid malignancies and how this can be manipulated to change the functions of malignant cells. We have found that histone deacetylase inhibitors promote apoptosis of some malignant cells but also allow the differentiation of other malignant cells, making it an attractive treatment option for myeloid malignancies.

Epigenetics is a very attractive therapeutic target as aberrant epigenetic patterns play an important role in disease pathophysiology and these aberrations are modifiable using clinically available drugs. Until now we have mainly

focussed on targeting one mechanism at a time, but more and more evidence points to higher efficacy of certain treatment combinations. It is likely that these combinations will soon be available and change the outlook of patients with myeloid malignancies.

Q5 Overall, you have more than 150 publications and have written several book chapters. What are you working on next?

At the moment I am involved in an ambitious educational project: the implementation of a new medical school. This medical school, born out of a partnership between the Portuguese Catholic University, Portugal; the Luz Hospital Group, Portugal; and Maastricht University, the Netherlands, proposes to introduce modern, student-centred learning methodologies and introduce students to clinical competences from the first year of medical school.

This is a large project and, as Founding Dean, I am involved in all aspects of the project, from recruiting teaching staff, designing and adapting curricula, setting up the whole medical school organisational framework, and ensuring compliance with national and European requirements. It is a project which definitely throws me out of my depth but holds great promise for the future.

Q6 As the chair of the curriculum committee for the EHA, what are your plans for future directions for learning and training in haematology?

The EHA has been pioneering in many aspects of haematology training. The European Curriculum was the first document of its kind, listing all the areas in which European haematologists should receive training. 'Hanging' on the backbone of the curriculum is a wide variety of learning materials, from webcasts of congress proceedings to expert interviews and important articles. But the online learning tools are continuously evolving and last year we inaugurated the Campus, with interactive content enabling self-assessment and progress evaluation. These include complete courses covering all aspects of a certain disease to brief clinical cases with problems to solve. Our plan is to increase and improve these materials so that our haematologists are ever better prepared for clinical practice.

As an important accreditation tool, we have implemented the European Exam, which is increasingly recognised as an added value to those who hold the title and is part of the official end of training assessment in Switzerland.

Q7 What strategies is the EHA looking at for delivering online teaching and learning, particularly as so many congresses have been cancelled this year or moved to online platforms?

EHA has already travelled a great distance on the path of online learning. The online library Learning Center is a rich repository of passive learning material; the Campus has highly organised material with many interactive features; and the masterclasses have group activities guided by mentors who stimulate peer-to-peer learning. The inevitable transformation of our annual Congress into a virtual event has been an exciting challenge. We have carefully selected a modern platform and have totally changed the structure of the congress to mould it to a virtual environment. Any more information would be a spoiler... I suggest everyone registers and participates!

Q8 What advice would you give to new haematology trainees or recent medical school graduates at the start of their careers?

Medicine is a fascinating and ever-new world. Keep an open and curious mind, grab opportunities as they appear, and be flexible. It is a fast-changing world and haematology is, as always, in the forefront.

Dr Noémi Roy

European Hematology Association (EHA) Guidelines Committee Chair
Consultant Haematologist at Department of Haematology, Oxford University Hospitals NHS Foundation Trust, UK, and an Honorary Senior Clinical Lecturer at the University of Oxford

Q1 What do you find most interesting about rare inherited anaemias and haemoglobinopathies?

It's a wonderful group of people and I love having a long-term relationship with the patients and their families. These are genetic conditions and often they affect different aspects of the red blood cells, such as globin and heme, or cytoskeletal proteins and enzymes that support red blood cell function. What I find fascinating is how one mutation in the β globin gene responsible for causing sickle cell disease can lead not only to such a multisystem disorder, but also the fact that individuals with the same mutation can have such different phenotypes. This can vary from a very mild anaemia to severe disease with multiple life-threatening complications such as stroke and acute chest crises. The challenge for coming years, as well as finding new treatments, will be to unpick the complex genetic and environmental modifiers which together determine, or at least influence, the disease phenotype. Even more intriguing to me are the conditions that result from mutations in genes that affect not only red blood cells, but in fact all cell types in the body. For example, Diamond–Blackfan anaemia arises from mutations in genes that code for ribosomal proteins, a key function in all the body's cells, and yet the red blood cells seem the most sensitive to perturbation. In congenital dyserythropoietic anaemia (CDA), mutations in proteins that act in the nucleus also have most profound effects on red blood cell integrity. Trying to understand how mutations in these genes cause disease will not only help us find new, better, and targeted treatments, but also give us important insights into how red blood cells normally develop.

Q2 Could you tell us about the challenges associated with working in the rare diseases field?

There have been some positive changes in the past few years where rare diseases are concerned. Following a European Union (EU) directive, the UK produced its Rare Disease Strategy in 2013 to improve the diagnosis, treatment, and management of all rare diseases. More recently, the formation of the European Rare Disease Networks funded by the EU has provided a structure for partners across Europe to work together on common goals. It has been very fruitful and satisfying to work closely alongside my European colleagues through the EuroBloodNet. Nevertheless, working in a rare disease field, and more generally working in non-malignant haematology, brings about a set of difficulties. Even the term is misleading, because for someone living with sickle cell disease having a stroke in childhood is as devastating as receiving a diagnosis of cancer would be to someone else. Funding for research is always an issue, and although some rare disease-specific funding exists, it can be difficult to attract long-term funding for some rare conditions. The greatest challenge, however, is getting the patients' voices heard. We have had some recent successes for rare inherited anaemias with the publication of a James Lind Alliance Priority Setting Partnership in Rare Inherited Anaemias.[1] It is important however that the priorities patients have identified are then translated into funded projects.

"It's a wonderful group of people and I love having a long-term relationship with the patients and their families"

Q3 How do you manage your time between your clinical and academic duties at the University of Oxford?

My role is more clinical than research at the moment, and I love having different aspects to my work: I do outpatient clinics in my hospital and in a larger region; I spend some time looking after the general haematology lab; I run the genetic multidisciplinary meetings for rare inherited anaemias; and I have a role within a larger team in how we organise and run our red cell service across a large geographical area. My research interests are spread across the rare disorders, in particular CDA-1 where I work closely with colleagues in the Weatherall Institute of Molecular Medicine. I am also involved in a number of projects that aim to refine how we treat a very common anaemia – iron deficiency – in different patient groups. I am also very interested in quality of life and in patient-led research, and I am trying to lead a quality-of-life study for people living with sickle cell disease called RUDY[2] all across the UK. Finally, I have a role in the organisation of the teaching and training of our haematology trainees, which I find very rewarding. As with any position made up of such varied duties, the key to being able to fulfil all of these roles is the requirement for fastidious organisation and much flexibility, with patient care always as the centre and priority.

Q4 Could you summarise the key take-home messages of your recent publication 'Majeed syndrome: description of a novel mutation and therapeutic response to bisphosphonates and IL-1 blockade with anakinra.'

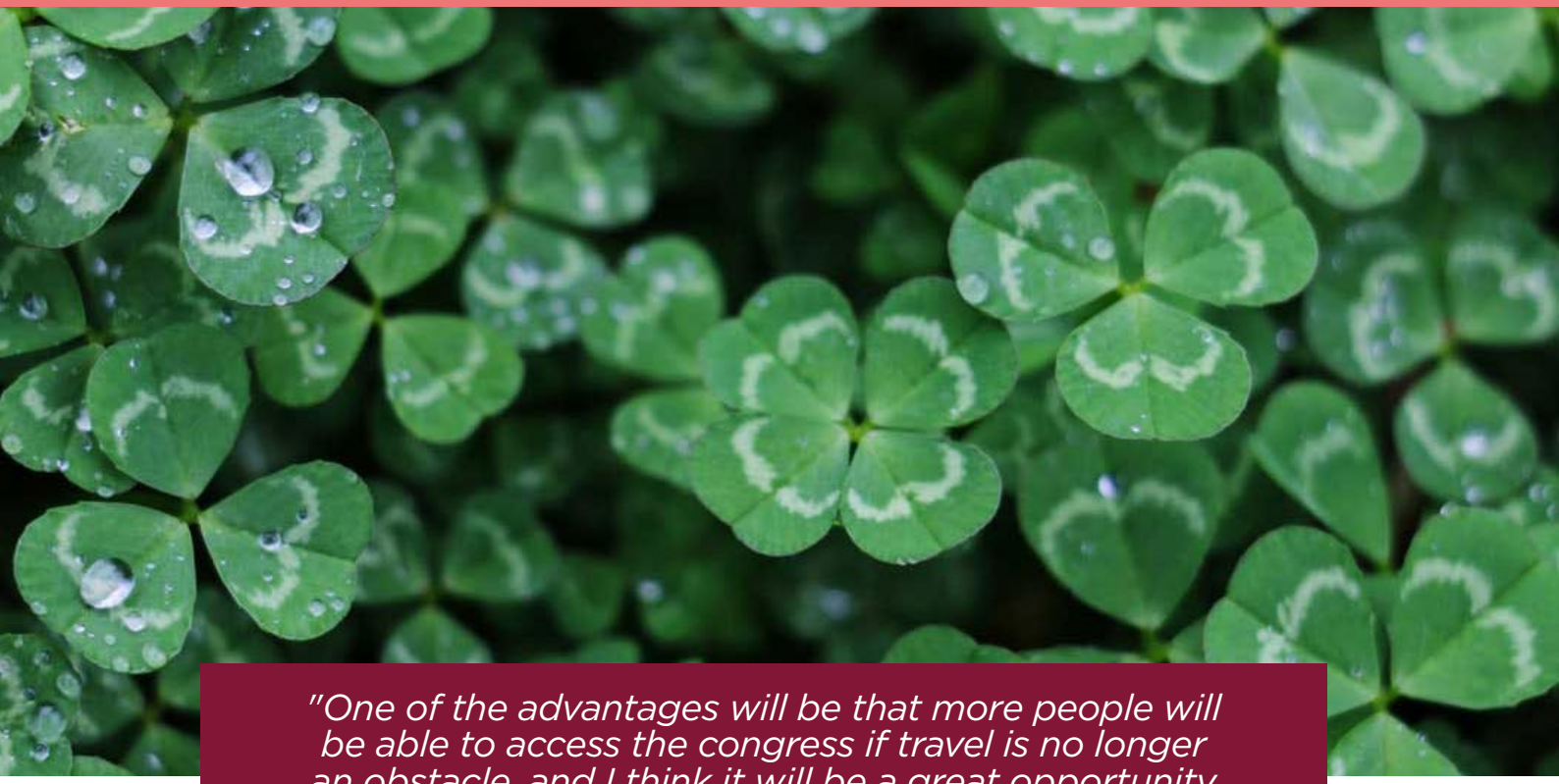
Having spoken about rare diseases, there is another category, ultra-rare diseases, which describes conditions in which there are fewer than 1:50,000 affected individuals. Majeed syndrome is one such condition, with only a handful of families reported worldwide. It presents as the combination of anaemia (specifically [CDA]), recurrent episodes of non-infective osteomyelitis, and skin manifestations. Although anaemia is a feature, the chronic recurrent multifocal osteomyelitis is the dominant aspect and the one that causes patients the most difficulties. The condition is recessive and due to mutations in a gene called *LPIN2*. The protein produced by this gene was known to be involved in fat metabolism, but quite how this could lead to recurrent inflammation let alone anaemia is still not entirely clear. The family that we studied not only had a new mutation in this gene, but showed widely different phenotypes between affected members, despite identical mutations. It is now becoming clearer that *LPIN2* plays a role in modulating and controlling the inflammasome which is responsible for IL-1 production. Blocking this process with an IL-1 receptor antagonist has clinical benefits for these patients.

Q5 Which element of your position as European Hematology Association (EHA) Guidelines Committee Chair do you enjoy the most?

Our committee works very efficiently as a team, and what has been so exciting is that we have all been there from the beginning as the EHA only just started commissioning guidelines in the past 2 years. It means we have had the opportunity to design the terms of reference and methodologies as a group. It's a great privilege to work with international experts in different sub-specialties of haematology and I have also found it interesting to learn more about the EHA structure, and in particular the wonderful breadth and depth of expertise that comes from the Scientific Working Groups. It has also been a wonderful opportunity to work with other societies to start thinking about the practicalities of producing joint guidelines. I am also quite interested in trying to think about including the patient voice in the process of developing guidelines, and in producing completed guidelines in lay language for patients to be able to access.

Q6 EHA 2020 will be a virtual congress this year. What benefits do you think this may have compared to the usual meeting?

Of course at the moment it is difficult to think positively about the fact that we will not be able to gather together in June as we do every year. We think with great sadness of our colleagues and friends who have died as a result of the COVID-19 pandemic, of those who continue to put themselves at risk by looking after infected patients, and of those who are working tirelessly in trying to develop a vaccine and to evaluate different treatments. Having said all of that, it's quite a challenge and



"One of the advantages will be that more people will be able to access the congress if travel is no longer an obstacle, and I think it will be a great opportunity for people who would not normally have been able to attend in person to access the presentations, posters, and discussions in this new format"

ambitious for EHA to put the congress together virtually and we are all looking forward to being able to see what new research is ready to be shared and discussed in this format. One of the advantages will be that more people will be able to access the congress if travel is no longer an obstacle, and I think it will be a great opportunity for people who would not normally have been able to attend in person to access the presentations, posters, and discussions in this new format.

Q7 EHA are hosting webinars related to the care of haematology patients during the COVID-19 pandemic. As Guidelines Committee Chair, could you tell us how the guidelines have been updated for these patients?

EHA has been very proactive from the very beginning of the pandemic in providing a trusted source of information for clinicians in these uncertain times. We cannot, by definition, develop guidelines in a new pandemic as these require evidence in order to make recommendations. However, numerous clinicians and scientists have been able to provide guidance based partly on some evidence and partly on expert opinion on the likely safe courses of action that should be taken in a variety of conditions. I believe this has been helpful to haematologists in many countries in trying to make decisions about which treatments to continue or stop, or how some treatment modalities should be modified to ensure both patient safety as well as efficacy against their underlying disease. In the Guidelines Committee, we have reviewed this guidance at short notice, sometimes multiple versions as the accumulating evidence or circumstances were changing. We will continue to do so as the situation evolves.

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Roundtable Interview with Dr Alba Maiques-Diaz and Dr Anna Kabanova

YoungEHA Committee Members

Dr Alba Maiques-Diaz
Postdoctoral Scientist, Biomedical Epigenomics Group, IDIBAPS, Barcelona, Spain.

Dr Anna Kabanova
Group leader, Toscana Life Sciences Foundation, Siena, Italy

Q1 What inspired you to specialise in haematology research over other disciplines?

Dr Maiques-Diaz: This was not something I planned. I ended up doing an internship during the last year of my university degree in a cytogenetics laboratory and got fascinated with the haematology field they were working on. From there onwards, I decided to stick to it. I am still fascinated with the fact that our body can constantly create millions of blood cells with specific functions and that it is done correctly. It is a fine-tuned system with many unanswered questions.

Dr Kabanova: Joining the haematology field happened almost by chance for me as well. I did my PhD and first postdoctoral studies in the immunology field, studying B cell responses to vaccination and infection. When I started a second postdoc, the hosting laboratory was collaborating with the haematology unit at the local university hospital. This is how I started my journey into the field of B cell malignancies. Here, I became fascinated with the multitude of existing experimental approaches that can be used to perform translational research and the variety of questions that you may address with them.

Q2 What is your current research focus, and what in your opinion are some of the most important areas of haematology research needing increased attention in years to come?

Dr Maiques-Diaz: My research focusses on understanding the role of transcription factors in driving blood tumours. I have studied them in acute myeloid leukaemia and have recently started to do so in chronic lymphocytic leukaemia (CLL). Transcription factors are like the directors of the orchestra, if they do not do their work properly the music will sound out of tune. Understanding the biology of transcription factors will help in finding therapies that target their 'Achilles heel' and inhibit their aberrant activity in tumours.

I believe that technology is very much driving research revolutions nowadays and a current big step forward is single-cell analyses. This will allow us to learn whether the entities we have created are homogeneous populations or if there is a strong cellular variability. This can change how we define and probably treat haematological diseases.

Dr Kabanova: My projects focus on CLL. In my work I aim to get a deeper understanding of gatekeeper circuits that help to keep tumour B cells quiescent. CLL is characterised by a high incidence of indolent disease suggesting that an active molecular network suppressing tumour progression might be in place. Our knowledge on this network and its regulation is relatively fragmentary; therefore, we aim to deepen it and use this knowledge to treat aggressive forms of CLL and potentially also other B cell tumours. In my work, I like to combine approaches at different biological scales. We are interested in studying micro-processes such as receptor signalling and organelle biology, while at the

same time taking advantage of omics technologies to analyse functional protein networks at the systems level.

Q3 In your opinion what attributes are necessary for being a successful translational scientist, and what would be your advice to fellow young scientists embarking on their careers?

Dr Maiques-Diaz: Nowadays science is moving fast and changing quickly. This means that on top of being curious, you should also work on being resilient and flexible. To be able to adapt and transform your research accordingly with new discoveries and technologies is essential. Being a translational scientist means that you need to gain a lot of knowledge and master many different abilities. Whether you come from a clinical or a biological background, you will need to learn a lot from both fields and ideally also become fluent in computational analyses. This is key! Be prepared to learn to code in R and to deal with lots of different data and software. I would advise young scientists not to specialise too soon and to learn as much variable knowledge as possible. Also, they should not forget to expose themselves to challenges and expand their professional skills. Those will be essential to have a fruitful career in the future.

Q4 How did you become involved with the YoungEHA committee and what was the goal you set out to achieve when you joined?

Dr Kabanova: I joined the committee by applying to an open call that I spotted on the EHA website almost by chance! The call was issued in the summer of 2018 and at the end of the year I got a reply from the EHA with an invitation to join the committee. Committee members, ongoing mandates, and the newcomers first met during the EHA24 in Amsterdam; that was a very lovely start!

My primary inspiration to join the committee was dictated by the fact that being a biologist and quite new to the haematology field with only several years of translational research in my background, I wanted to get to know haematology peers better. Furthermore, I was really interested in understanding how scientific associations and committees work and to get involved in various activities such as the EHA Congress organisation. In reality, the activities turned out to be much more diverse than expected. Every committee member is free to choose the type of activity that has the most affinity with his or her own interests and background. I chose to bring some personal 'fresh' experience of being a mum and an active researcher to the YoungEHA. Having found an affinity in this aspect with some other members of the committee, including Dr Maiques-Diaz, we set off to implement some changes to the current EHA criteria for grant eligibility and congress participation to provide more support to parenting researchers. Our initiative has resulted in the uptake of childcare facilities during congress (which can't be experienced yet due to the COVID-19 pandemic in 2020) and the implementation of a change in eligibility criteria across all EHA Talent Acceleration programmes (mentoring programmes and research grants). This is only an example of how a personal experience could drive the involvement in committee activities. Luckily, EHA gives space to the YoungEHA committee members to propose new ideas. We feel great support which is very inspiring and drives us to set new goals.

Q5 What is the mission of the YoungEHA committee, how does it contribute to the annual congress, and what are some of your typical roles?

Dr Maiques-Diaz: The mission of the committee is to represent the voice of early career researchers and clinicians in haematology within EHA. We are an inclusive community that aims to inspire young haematologists and help them to achieve their full potential. Our team has grown in the last 2 years and we are now 13 members and ambassadors actively working together representing different European countries including Italy, Spain, Germany, the Czech Republic, Bulgaria, Belgium, and the Netherlands. The space EHA is giving juniors is expanding and this is indeed a great opportunity to raise the needs of junior researchers, clinicians, and other young professionals involved in haematology. One concrete example of our results is a future launch of a new training programme in bioinformatics which will join the existing EHA Clinical Research Training in Hematology and EHA Translational Research Training in Hematology programmes. We have a voice now

and are working together with the EHA Board and the rest of the EHA committees to promote this and other activities for the benefit of the YoungEHA community.

We are heavily involved in the organisation of the annual EHA Congress, co-organise the YoungEHA Experimental Research Meeting (YERM) together with local researchers from the area of each year's meeting, and the Young EHA track. In these sessions we aim to highlight research topics that are a bit different than the rest of the congress, either because they have a more flexible format, or because we cover topics that are not as well represented. Usually, these topics look at new developments in or outside of haematology that are of use to haematologists. For instance, this year artificial intelligence and the effects of nutrition and microbiome on haematological outcomes will be discussed. The YoungEHA track is meant to inspire and to educate.

Q6 What could research associations such as EHA do to support haematologists during the pandemic?

Dr Maiques-Diaz: Research associations are very much needed at this moment. We are going through difficult times where we feel isolated and the anxiety and stress levels are rising together with the uncertainty we are going through. I believe research associations should work to build communities and networks. We now need to feel connected more than ever, feel that we are not alone, understand that other people are going through the same issues, and also be able to exchange scientific and clinical information in a safe and professional environment. Particularly for us juniors, still in the process of building our career, it can be emotionally damaging to feel alone at home and not being able to do our laboratory work or to take care of our patients properly. Building supportive networks between peers is essential to overcome these difficulties and to transform challenging situations into strategies that will help us to feel empowered.

Q7 EHA has now launched the COVID-19 EHA Hub which is driven by the YoungEHA committee members. Could you please tell us more about these initiatives?

Dr Kabanova: The EHA Hub[1] was launched online at the end of March, roughly a month after COVID-19 first hit Europe. The creation of the Hub was initiated and driven by the YoungEHA committee, and the idea behind it was to provide a virtual space for haematology professionals and researchers to discuss challenges, share relevant information, and find support, both professional and psychological, if needed. The impact of COVID-19 globally is massive. Patients, clinicians, and researchers are all impacted by this situation. Therefore, the Hub was devised to help join forces and collaborate as a community. The Hub is organised in different sections, grouping the different topics in a useful way, including guidance and publications, case reports, personal protective equipment and ethics, research ideas, and coping and sharing. Many haematology professionals are currently using it to share and exchange.

Q8 YoungEHA has conducted a survey to understand the challenges researchers are having associated with the lockdown, can you share with us highlights of the answers?

Dr Maiques-Diaz: We started this survey as we wanted to understand the main challenges the young haematology community is going through and to use this information for the special webinar[2] for researchers on 30th April. This webinar was part of the EHA COVID-19 webinar series[3] that aimed to create a space where both clinical and translational/basic researchers could share the ideas, views, and strategies they were using to cope with the lockdown and to plan reopening their laboratories. We are still analysing the data from the survey and aim to publish this as soon as possible, but the answers are already interesting.

Out of the 215 responses we got, only 17% of the respondents consider themselves having similar productivity to before the lockdown. There were no major differences between biologists (with a PhD) or clinicians (who do research) in how productive they are feeling, and most of the people (42% of the responses) consider themselves being 0–40% productive. The reasons for the loss of productivity are "not being able to do experiments" or "to use relevant facilities to work." Many people also stated that this was due to "having to take care of the children as they have no child-care" or that "the stress/anxiety of the situation make me less productive." We still need to analyse whether we observe different answers between junior and senior researchers

or between the different countries we got the most responses from (Italy, Spain, UK, USA, and Germany) where the lockdown policies were different. We also asked about research funding and this is a topic that resonated with many people. This is a complex issue as each country has different funding strategies, but overall many people were unsatisfied with the information they got from their funding agencies. Which is already something to think about.

Q9 What is your favourite aspect about the EHA congress and what are your thoughts on EHA25 VIRTUAL?

Dr Kabanova: For a translational researcher, the EHA congress is a great opportunity to improve one's knowledge on the clinical side of pathologies that we are working on. Additionally, being extremely broad and filled with events, one can always find an interesting and inspiring talk to listen to. Being involved in the organisation of the YoungEHA track and YERM meetings, we all really enjoy listening to the speakers and participating in the professional-skills session. At EHA24, the YoungEHA voice was definitely heard and catered for.

The fact that EHA25 will become virtual was met with great joy. First, it meant that fortunately the congress was going to happen despite COVID-19 which is already a great achievement since many research meetings scheduled in 2020 were cancelled. Second, it gave the YoungEHA committee and the EHA an exciting possibility to evaluate two interesting ideas: 1) can we make the EHA Congress available to more participants since virtual platforms lower the costs of the meeting attendance and 2) is there a possibility to translate a part of future EHA congresses to the virtual space or maybe hold 'live' and 'virtual' congresses in parallel. We are very curious to receive feedback from EHA25 participants and see how this will shape the future organisation of EHA congresses.

Q10 COVID-19 has forced many countries to lockdown and thus a lot of research has been stopped, what are you doing to adapt to this situation?

Dr Maiques-Diaz: Adapting to being at home and working with a computer when you are a wet-lab researcher who loves doing experiments is not easy. I have recently moved to a new laboratory and it took over 1 year to have experiments running appropriately and to start answering some of the questions we have. This was just happening when the lockdown came. We had to change gears and redefine new objectives. I need to work with a direction that is divided into small objectives and tasks, to feel the progress, and not get lost. Finding new directions is what has worked for me. I was able to identify two major goals to do these months. First to finish a manuscript I have pending from my former laboratory and second to do further computational analysis to define in more detail the project we are starting. During these months, the latter is also helping the PhD student I supervise to start learning computational biology, something that she will heavily benefit from. On top of this, I feel that holding laboratory meetings to discuss projects from laboratory mates and to keep connected is also emotionally essential.

Dr Kabanova: My story is very similar to that of Dr Maiques-Diaz, with the difference that after a period of lockdown our institute has gradually reopened its doors. Since May we have been back in the laboratory with the limitation imposed by the security conditions to work at a reduced number of personnel. We have also had some uncertainty with starting the internships for new students and signing contracts for the new members of the laboratory. These challenges are shared by many laboratories around the world. Luckily the funding agencies that provided me with a start-up grant provided the grantees with the necessary flexibility such as no-cost extensions and allowance for free budget reallocation. This flexibility and more funding support, to protect 'vulnerable' groups and vulnerable fields of research, is what is now needed. A response should be immediate to avoid long-term consequences of the lockdown for many years ahead.

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Pregnancy-Related Thromboembolism in Sickle Cell Disease

EDITOR'S PICK

Sickle cell disease is a blood disorder that shortens life expectancy and research is currently lacking on pregnant females with the condition. This review considers some of the most important aspects of pregnancy-associated sickle cell disease and thromboembolism, the present understanding of the disease, pathology, clinical issues, recent therapies, and clinical management of both mothers and fetuses. Pregnancy in sickle cell disease is an emerging issue requiring attention and education activity in Europe. Therefore, it is very important that this review article is widely distributed.

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Abstract

Haematological disorders are predominant in the tropical and subtropical countries where major problems of sickle-cell disease (SCD) and thalassaemias are often recorded. However, reports of these conditions have increased in the Western hemisphere more recently. Genetic counselling, early detection of the disease condition, and determining an appropriate treatment regimen remains the solution. Most molecular types of SCD have been determined and the pathological impact of individual types along with the degree of severity is known to clinical investigators and physicians. There is, however, a significant need for a proper counselling system for the clinical diagnosis in most countries. Lack of funding, trained personnel, relevant physicians, instruments, and laboratories are the challenges to overcome. Pregnancy-associated SCD and thromboembolism require special mention due to their mortality rate, complexity of treatment, and care necessities. This review considers some of the most important aspects of pregnancy-associated SCD and thromboembolism, shedding light on the present understanding of the disease condition, pathology, clinical issues, the association with venous thromboembolism, recent treatment measures, and clinical and social management of pregnant women and fetuses for patients with SCD. Integrated social and clinical care along with extensive timely medical and clinical counselling for patients can improve the present situation which is growing in different countries. To save future generations and pregnant mothers from the haematological disorders that could be either prevented or treated, essential genetic screening or counselling should be made a priority by governments. In addition, social education and campaigns related to the disease condition can help to improve the situation.

INTRODUCTION

The growth of the human population could be attributed to better healthcare facilities and medical management. Management of regular health concerns including pregnancy and neonatal management has become more efficient with time. Yet, maternal morbidity, especially because of a specific condition such as sickle cell disease (SCD), is considerable. The impact is tremendous in developing countries including the Sub-Saharan region, Middle-Eastern countries, Asia, and Latin American countries. The estimated global burden of sickle cell anaemia in children under 5 years of age could become 500,000 cases by the year 2050.[1] Unfortunately, the burden of SCD is high in Nigeria, the Democratic Republic of Congo, and India. Specific countries have high risk of child or maternal death caused by SCD; for example, in French Guiana, one in every 235 children is affected by such a genetic disorder.[2]

Sickle Cell Disease

In SCD, red blood cells (RBC) are crescent-shaped, restricting blood flow in the narrow blood vessel and causing tissue damage and pain. SCD is an autosomal recessive genetic disorder. Haematological and genetic analyses suggest that there are many forms of SCD due to various homozygous genotypes, haemoglobin S (*HbS*), and the different heterozygous states of haemoglobin C. There are several subtypes, including haemoglobin SS, haemoglobin SC, haemoglobin SB+ (beta) thalassaemia, haemoglobin SB 0 (beta-zero) thalassaemia, haemoglobin SD, haemoglobin SE, and haemoglobin SO. Those who inherit the mutated HbS gene from one parent may not have many health issues and are considered as having sickle cell trait (SCT). Thus, patients with the SCT serve as a carrier of SCD with a single copy of the mutated gene. Patients mostly remain asymptomatic and lead a normal life; however, patients with SCD have both the mutated genes, are symptomatic, and display some or all clinical signs associated with the disease. Presentation of these symptoms varies from patient to patient depending on their demographic, clinical, and other factors.

SICKLE CELL TRAIT AND PATHOLOGY

The predominance of sickle cell anaemia in different regions of Africa is due to the abundance of SCT in the population that naturally aids in surviving malaria.[3] SCD occurs as a result of a point mutation in the gene for beta-globin where *Glu-6* is altered to *Val-6* promoting the production of HbS. Such abnormal haematological conditions reduce the natural lifespan of the population due to one or the more severe complications.[4] Patients with these conditions also tend to have a higher epidemiology of venous thromboembolism (VTE);[4,5] therefore, an increased trend should be observed in pregnant women in these populations. Interestingly, a recent study on pregnant women and the increased trend of VTE in pregnancy and postpartum suggested no difference in the occurrence of pulmonary emboli or other VTE in pregnant women with SCT compared to women who did not have the condition.[6] However, special attention should be given to pregnant women with SCT. Although SCT is an apparently benign state, it requires proper diagnosis for future generations and possible differentiation with beta-thalassaemia. A detailed analysis to differentiate between the thalassaemic and SCT condition should be opted for before confirming SCT.[7] SCT is not always harmless: certain conditions of SCT can invoke thrombosis.[8] Moreover, adequate facilities and training for medical practitioners are required to tackle any general or emergency situations to manage complications that may arise.[9] Advanced monitoring and detection technology such as optofluidic resonator-based methods may help in the timely detection of SCD conditions.[10] Although there is population-specific evidence for increased risk of SCD or SCT, global estimation of the disease reports otherwise where higher prevalence of the disease condition was noted for the African–American population, Saudi Arabian population, among others. Consequently, SCD and SCT have become a global challenge for researchers and medical practitioners.[11,12]

SCD presents with a homozygous gene mutation: a mutation in both alleles. Microscopic, physiological, and biochemical analyses suggest that the RBC shape alters to a sickle or crescent shape due to the mutation and the possibility of clump formation increases manifold, forming

blood vessel blockage, consequently impeding normal blood flow. These physiological events present pain and affect blood pressure. Moreover, the life span of sickle cells is only 10–20 days compared to the normal lifespan of a RBC which is 120 days. Production of RBC by the bone marrow is impacted and there is an acute reduction in RBC number.

Patients with SCT generally do not show any symptoms; however, the condition can be worsened by certain factors such as severe dehydration, physical exertion, and high altitude where the oxygen level demands increase. The established and prominent diagnostic symptoms of SCD are manifestations of bone marrow infarction, this may include mild to severe bone pain, avascular bone necrosis, painful crisis, hypersplenism, cerebrovascular accident, splenic sequestration, meningitis, septicaemia, aplastic crisis, and others.

The blood coagulation system alters in patients with SCD. A variety of biochemical markers associated with thrombin and fibrin generations such as fibrinopeptide A, thrombin–antithrombin complexes, plasmin–antiplasmin complexes, prothrombin fragment 1.2, and D-dimer levels augment in the blood plasma and activate the coagulation process. Assessment of these markers with thrombin generation assays and thromboelastography also confirms alterations that promote the prothrombotic state.

ASSOCIATED HEALTH ISSUES

Common health problems associated with SCD are severe anaemia caused by extensive haemolysis and the short life span of sickle cells, hand–foot syndrome caused by swollen limbs from poor blood flow, splenic sequestration caused by restricted blood flow and an enlarged spleen, hampered growth and maturation, seizures and similar neurological conditions caused by lack of blood flow in brain, heart and lung conditions including pulmonary hypertension, pulmonary fibrosis, and severe heart problems.

PREGNANCY AND SICKLE CELL DISEASE

The physiological changes during pregnancy induce several complications for the mother and the child due to the presence of SCD. Both antepartum and postpartum complications are reported frequently where SCD is associated with pregnancy. Altered metabolism and vasculature in the mother and child further increases the risk of thromboembolism.

Increased metabolic demand, blood supply, blood viscosity, and coagulability can induce complications of SCD in the mother with predominant clinical issues such as thromboembolism, ulcers, and heart and lung issues including pulmonary embolism and infarctions. Necrosis and vaso-occlusive crisis remain the primary manifestations in these cases. All of these clinical conditions may restrict the uteroplacental circulation which is vital for fetal survival. Fetal hypoxia and further complications are the subsequent issues that may arise for pregnant women with SCD.[13] During the gestational period, frequent and repetitive episodes of pre-eclampsia and eclampsia are common due to SCD and impaired circulation.

Excessive risk of maternal morbidity is reported in Jamaica and Saudi Arabia because of unmanageable complications of SCD. The estimated risk factors are relatively high and unexpected due to the association of a number of complications that elevate the morbidity rate.[14-16] Estimated association analysis of maternal outcomes and SCD suggested that there is a higher relative risk for the mothers having SCD compared to the general population and almost twice the risk of pre-eclampsia. Additionally, association analysis of neonatal outcomes and SCD suggested the increased risk of neonatal death along with increased complications for the mother.[17]

VENOUS THROMBOEMBOLISM AND PREGNANCY

VTE is directly associated with SCD, especially in pregnancy. Unfortunately, VTE is triggered during pregnancy and the impact remains severe due to the onset of deep vein thrombosis or pulmonary embolism. Lim et al.[18] reported

that VTE can affect one in 100,000 women at childbearing age in the general population, whereas approximately 500 per 100,000 individuals are affected in an older age group.[18,19] Although VTE is associated with older age, a considerable number of cases of VTE are associated with pregnancy.[20] This condition is probably induced by eclampsia, pre-eclampsia, and other associated complications. Antepartum and postpartum pregnancy-associated VTE was reported to occur in 59 out of every 10,000 pregnancies by Coon et al.,[20] however, the risk of VTE is quite low (2 in every 10,000 per year) in women who are not pregnant.[21,22] Previous assessment through CT pulmonary angiography suggested no difference between patients with SCD and the general population in the case of acute pulmonary.[23]

Research outcomes have revealed that in pregnancy, plasma fibrin and D-dimer increases with the progressive gestational age for mothers who are sickle cell carriers, mostly having African and South Asian ancestry. Therefore, fibrin-associated markers, fibrin monomers, or D-dimer could be useful indicators for VTE in women with SCD-associated pregnancies.[24]

MANAGEMENT OF SICKLE CELL DISEASE IN PREGNANCY

SCD-associated pregnancy can result in multiple complications including premature labour, severe pain, restricted fetal growth, and mortality. Spontaneous miscarriage is another unfortunate outcome that occurs frequently.[25,26] Therefore, the pregnancy of patients with SCD should be handled delicately by medical care providers. Information on dehydration, cold, hypoxia, and their relation to SCD should be explained properly to the women who are planning to conceive. Detailed information on the plausible adverse outcomes should also be explained and embolism-related issues should be discussed. Vaccination status should be decided carefully by the medical practitioners, with special consideration given to concerns regarding thromboembolism. Antenatal haemoglobinopathyscreening is mandatory to track conditions. Routine prophylactic blood transfusion should be avoided for patients with SCD; moreover, matching blood type should be completed for extended phenotypes as well as Kell typing to aid in an emergency. Special care should be taken for acute chest syndrome, pulmonary embolism, painful crisis, and other complications.

TREATMENT AND THERAPY

Pregnant women with SCD and VTE should be treated with specific care. Modern diagnostics tools such as compression ultrasonography can be used for assessment of the legs and CT pulmonary angiography can be used for assessment of the lungs. Depending on the outcomes, anticoagulant therapy or other further diagnoses can be made. A novel treatment approach for SCD is highly necessary. Growing research efforts in this direction may yield the expected outcomes. Sphingosine-1-phosphate hampers the oxygen-binding affinity of HbS through structural conformation change as reported by Sun et al.[27] Metabolic re-engineering may lead to novel therapeutics based on the function of sphingosine-1-phosphate.

Assessment of pregnant patients and proper prophylaxis remain the key to proper and safe outcomes. Varying recommendations based on the specific conditions are available depending on the facility and experts available. The regular screening of pulmonary hypertension, blood pressure, urine, retinal function, and iron overload is important. Additional care for possible urinary tract infection, sepsis, and pneumonia should be also considered during regular monitoring. Depending on the condition, penicillin prophylaxis or erythromycin are prescribed. When caring for these patients who are pregnant other factors such as premature labour, perinatal mortality, fetal growth, pain crisis, and delivery via caesarean section should be considered with cautious assessment of the consequences. As previously mentioned, prophylactic blood transfusions are generally avoided. A detailed analysis with a comparison between prophylactic and selective blood transfusion is reported by Okusanya and Oladapo.[28] They have recommended the comparison as inconclusive and suggested that the transfusion process is largely dependent on factors such as blood typing and grouping, cross-matching, and organisational capacities. A report by van Zuuren and Fedorowicz[29] gave the comparative use and relevant outcomes of using

low molecular weight heparin during the vaso-occlusive crisis in pregnant women with SCD. Tinzaparin and dalteparin were found to have a good effect on pain reduction and diminishing the hospital stay. Week-long thromboprophylaxis using low molecular weight heparin for normal delivery and 6 weeks for caesarean delivery was recommended.[13] Even after extensive care and situation handling, the pregnancy with SCD is high-risk and related outcomes for the patients having SCD are comparatively poorer than in the general population.[2,30] The evidence is available on low gestational age associated with VTE.[31] VTE was also associated with the delivery time and postpartum conditions in women.[32] Hence, all these additional complexities further warrant special care for pregnant women with SCD.

CONCLUSION AND FUTURE PERSPECTIVES

The growing number of cases of pregnancy with SCD and its mortality rate requires attention from medical practitioners. Better and improved treatment regimes have provided some improved outcomes in this aspect. The number of possible complications is substantial and requires multidimensional strategy and management. Further development of novel therapeutics and diagnostics can help in managing the complications and yield better outcomes by reducing the mortality rates of pregnant women and neonates.

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Initial Anticoagulant Management of Deep Vein Thrombosis/Venous Thromboembolism in Primary Care: Review of Current Approaches

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Abstract

Background and Aims: The initial management of deep vein thrombosis is starting to happen in general practice. New treatments are available to allow this shift, but guidance is variable. The aim of this study was to understand current choices used in general practice in the UK and to determine if there is a more efficient treatment, considering variability observed locally.

Methods: A systematic literature review and freedom of information requests to England's 198 clinical commissioning groups (CCG) were used to gather information on treatment options and current uses, respectively. Over 100 papers were assessed, and information from 177 CCG was obtained.

Results: There is noninferiority between injectable low-molecular-weight heparin and novel oral anticoagulant treatments. Fifteen CCG offered variable, but also limited, options of treatment. Patient choice was not necessarily considered.

Conclusion: There is variability in England on availability and choice of therapy for the initial management of deep vein thrombosis at present, which may also be the case elsewhere. The implementation of evidence-based guidelines should be carefully considered in all settings and countries.

INTRODUCTION

Healthcare continuously evolves, which requires the reassessment of management pathways based on new drugs becoming available and on clinical factors. When considering new medications, the costs and the efficiency are the main influences. Clinical factors include the costs of different pathways, the willingness to change paths from one setting to another, and the training required so that safety is not affected, among other factors. Patient choice should also be considered to make it easier to access the treatment needed, and to opt for different therapies with different monitoring needs. In a pandemic, like the current COVID-19 pandemic, a therapy not requiring regular blood testing of vulnerable or infected patients would be superior, but it is likely the decision would have been

taken beforehand, without considering this now-important risk.

There is an appetite to transform current healthcare pathways by enhancing community services in England,[1] for example, to prevent accident and emergency attendance and hospital admission of patients presenting with a possible deep vein thrombosis (DVT). In the future, suspected venous thromboembolism (VTE) management could follow similar pathways. If more were done in primary care, an improvement of patient experience as well as health outcomes would be expected.[2] DVT prevalence is approximately one per 1,000[3] and, consequently, is not a common presentation to general practice. Clear guidance is paramount, and evidence behind the choice of anticoagulant initiation treatment and attitudes among primary care physicians need to be considered. Variability of treatment exists as in Leeds, the CCG recommended tinzaparin in their pathway for the initial management of DVT, while less than 20 miles away, Bradford CCG recommended rivaroxaban.

According to the National Institute of Clinical Excellence (NICE),[4] initial treatment should include: "an interim 24-hour dose of a parenteral anticoagulant (if a proximal leg vein ultrasound scan cannot be carried out within 4 hours)," but the advice does not include novel oral anticoagulants (NOAC), which are also indicated for DVT or VTE treatment (such as apixaban[5] and rivaroxaban).[6]

As part of the feasibility of this study, the Cochrane library was accessed. Five Cochrane reviews with "deep vein thrombosis" and "initial treatment" in the title, abstract, or keywords were found. Three reviews focussed on pentasaccharides[7,8] and non-steroidal anti-inflammatories,[9] which are not among the therapies suggested by NICE nor available in the pathways promoted in primary care in the UK. A fourth paper[10] focussed on heparins alone, including subcutaneous unfractionated heparin (UFH), intravenous UFH, and low-molecular-weight heparin (LMWH), finding no difference among them. The last paper, on treatment at home versus hospital management,[11] focussed on LMWH and showed no clear differences in outcomes based on location of treatment. These five works did not provide answers to the issues at hand. The aim of this review was to determine what are the best options for the initial management of DVT in primary care, considering NOAC in particular, and to combine a systematic literature review with an assessment of the current practice in England. The rationale was that a combined approach would put theory and practice together, so that more robust conclusions would be obtained.

METHODS

An initial attempt utilising the PubMed and Medline databases for keyword searches of "deep vein thrombosis," "initial treatment," and "primary care" yielded only two results, one regarding attitudes[11] and the other in German. The authors then searched for the association of "deep vein thrombosis," "initial treatment," and "anticoagulant" in the NICE healthcare databases advanced search. A total of 195 articles were found among four of the databases accessed (cumulative index to nursing and allied health literature [CINAHL], EMBASE, Medline, and PubMed), although after duplications were removed 89 potential papers remained. Firstly, 19 papers were excluded as they were over 20 years old and would not adequately reflect current therapies, 18 were excluded as they were simple abstracts or posters from conferences and provided little information, seven papers were excluded due to a language barrier (three in German, two in Polish, one in Japanese, and one in Russian), and one paper was misquoted on the database and was not accessible. Finally, 21 papers were excluded as the subjects of the studies were not related to DVT drug management comparisons (Figure 1). As a result, 23 documents were obtained and further assessed, including accessing referenced papers. There were a variety of papers that provided insights for the study.

Simultaneously, freedom of information requests were sent to 199 clinical commissioning groups (CCG) in England to understand whether new pathways, like for the initial management of DVT, had been provided for general practice in the area. The standards for quality improvement reporting excellence (SQUIRE) checklist[13] was the most appropriate tool available for this type of project and was used to support the manuscript structure.

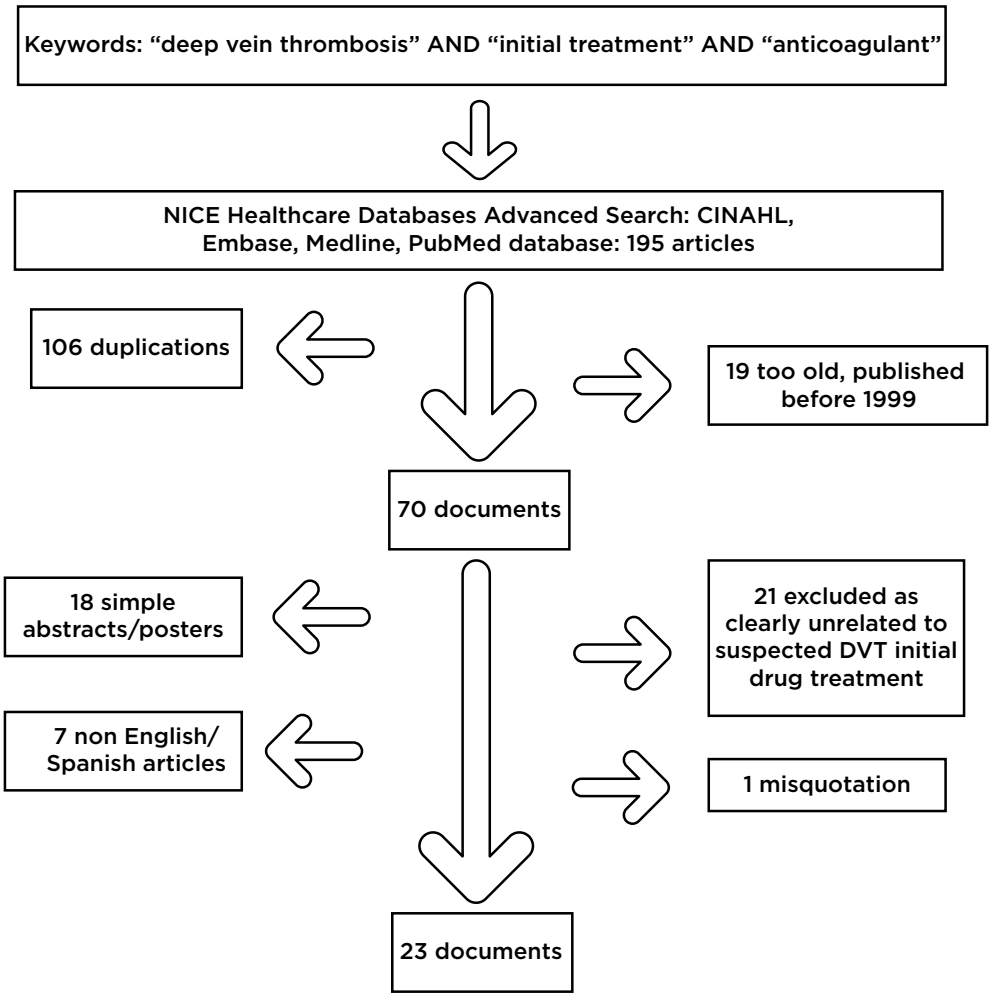

Figure 1: Flowchart of literature review paper selection process.
CINAHL: cumulative index to nursing and allied health literature.

RESULTS

The papers were studied in chronological order, looking first at long-established therapies and later at new medications available. This reflected the concept that evidence-based clinical practice is in continuous development, that guidelines need to be reviewed endlessly, and that even the way treatments are compared needs to evolve.

Introduction: Long-Established Therapies

In 2000, Douketis et al.[14] focussed on factors that made recurrent VTE more likely to occur, such as the presence of cancer, chronic cardiovascular disease, chronic respiratory disease, or other clinically significant medical disease. The treatment options in that study were only UFH or a LMWH, followed by warfarin. Chong[15] and Wells[16] described similar management alternatives; they focussed on the possibility that home treatment with subcutaneous LMWH could be as effective as intravenous UFH. Furthermore, Harenberg[17] concluded that LMWH was superior to intravenous heparin, and Hull and Pineo[18] concluded that UFH should no longer be standard therapy, replaced by LMWH. NOAC were not part of the available therapies at the time.

Huisman and Bounameaux,[19] as well as Schulmann,[20] assessed the benefits of LMWH and considered the benefits of a new oral medication, ximelagatran, but this medication was later withdrawn due to hepatic toxicity.[21] A systematic review by Akl et al.[22] considered

that among patients with cancer, LMWH was probably superior to UFH. Initial anticoagulation for patients with confirmed or highly suspected DVT, according to the American College of Chest Physicians evidence-based clinical practice guidelines from 2008,[21] included short-term treatment with subcutaneous LMWH, intravenous UFH, monitored subcutaneous UFH, fixed-dose subcutaneous UFH, or subcutaneous fondaparinux. There was no preference indicated. Not long after, it was accepted that LMWH had taken over from UFH as the initial treatment of choice.[23,24]

Novel Oral Anticoagulants

In 2010, NOAC were undergoing trials and expected to soon be in the market.[24] They included dabigatran, targeting thrombin (factor IIa), and apixaban and rivaroxaban, targeting factor Xa. By 2013 there were limited data about NOAC to allow for recommendation of their use to treat VTE in patients with cancer.[25] Rivaroxaban, apixaban, edoxaban, and dabigatran were considered to have similar efficacy and safety to conventional standard-of-care anticoagulation. Because of this, according to McRae,[26] clinical judgement regarding the optimal choice of anticoagulant therapy for VTE should have been based on individual patient characteristics. NOAC were not commonly used, and the main reasons preventing their use were cost-effectiveness and lack of a reversal agent.[12] Interestingly, Maervoet et al.[27] considered rivaroxaban a cost-effective therapy.

With improved safety and effectiveness of medications like rivaroxaban[28] and edoxaban[29] compared to standard anticoagulants, NOAC were positioning themselves where LMHW had in comparison to UFH eight years earlier, and physicians conservatively increased their use of NOAC instead of LMWH.[30] In Europe, the initial VTE treatment was parenteral heparin in approximately 66% of cases, while NOAC monotherapy prescriptions represented approximately 19%.[31]

Another issue reflected in the literature was the switching of anticoagulant treatment once initiated as, for example, one analysis noted that among patients with cancer: "Approximately one-quarter of patients who initiated on LMWH switched to other anticoagulant agents during the course of treatment compared to 8% and 5% of patients observed with warfarin and rivaroxaban respectively."[32] Turple et al.[33] suggested that physicians prescribe standard anticoagulation to many higher-risk patients before starting rivaroxaban. It was also noted that switching to rivaroxaban did not appear to adversely affect treatment outcomes, despite the greater presence of risk factors in those who were switched early.[33]

Although NOAC were not commonly prescribed in a paper by Mausbach et al.,[34] it was concluded that ambulatory treatment was safe. Guidelines were changing and NOAC were considered the first-line therapeutic agent instead of warfarin.[35] There were still specific groups of patients where LMWH remained the anticoagulant of choice, namely pregnant women and patients who are obese.[36]

Pathways in Practice

Several CCG in England have pathways that allow patients to start anticoagulation in primary care while waiting for confirmation of the diagnosis in secondary care. Using freedom of information requests to CCG, the number of CCG implementing community services for the management of DVT was identified, and the variability of approaches regarding the choice of anticoagulation noted. Among the 177 CCG that responded, only a few had pathways that involved general practitioners prescribing the initial anticoagulation. Three CCG had an injectable therapy as the initial anticoagulation: enoxaparin in Ipswich and East Suffolk CCG, and tinzaparin in Leeds CCG and Telford and Wrekin CCG. NOAC were the recommended initial therapy in the pathways of 11 CCG: apixaban in Brighton CCG and Sunderland CCG; apixaban or rivaroxaban in Eastern Cheshire CCG, Hambleton, Richmond, and Whitby CCG, and Northumberland CCG; rivaroxaban in Bradford CCG, Greater Huddersfield CCG, Harrogate CCG, Kernow CCG, and Wiltshire CCG; and a non-specified NOAC in Portsmouth CCG. One CCG pathway provided the option to choose an injectable or NOAC therapy, in County Durham and Darlington CCG.

Globally, NOAC have been widely used with or without a parenteral anticoagulant lead-in, but this varies geographically;[37] recent studies showed that NOAC were given to approximately

60% of patients on anticoagulants in Europe and Asia, but were given to <30% in Latin America and the Middle East.[38] Use of NOAC also depended on subpopulations of patients,[37] as they were less frequently used among patients who had cancer, chronic renal disease, heart failure, or prior stroke,[38] despite the efficacy and safety of NOAC being similar to,[39] or better than,[40] LMWH in patients with cancer, for example. NOAC use in specific populations remains challenging, such as in Asian populations or patients with cancer.[41]

DISCUSSION

This study combined an extensive literature review with freedom of information requests on current practice in England. This unique approach provided an understanding of which evidence-based VTE management is practised, and specifically which initial treatment of DVT is used in primary care in the UK.

Summary

Initial management of DVT no longer needs to be hospital based. New developments in pharmacology with LMWH and NOAC have allowed general practice to step in and offer patients a service that is more convenient. Looking at the literature available, it is clear there has been a progression of the options available for the management of VTE, and there is non-inferiority between LMWH and NOAC. However, the updated Chest guidelines[42] make a distinction for choice of therapy for patient subgroups: for patients without cancer, dabigatran, rivaroxaban, apixaban, or edoxaban are recommended, while if the patient has cancer-associated thrombosis, the first-line therapy is LMWH. Also of note is that initial parenteral anticoagulation should be given before dabigatran and edoxaban, but not before rivaroxaban and apixaban.[42]

General practitioners in the UK follow pathways designed locally, and in this study CCG approach was variable. Only one of the 15 CCG offering primary care DVT pathways allowed the possibility for choosing injectable therapies or NOAC, while the others were more restrictive. Considering that there is no inferiority among the different options currently available, these pathways could better accommodate patient choice.

Deciding between oral and injectable therapies is likely important to patients, but it was considered by only one of the CCG. Benefits of NOAC, including predictable dose response, lack of need for monitoring, reduced need for drug adjustment, absence of food interactions, and limited drug interactions,[43] would probably attract more patients compared to short-term injectable therapies with a probable switch to warfarin. In the long run, quality of life was comparable between NOAC and warfarin therapies but NOAC treatment resulted in higher treatment satisfaction;[44] the fact that regular monitoring is required with warfarin was an issue probably not fully considered. Discussion of monitoring requirements with patients should include risks associated with mobility and travel changes, because of shielding or self-isolating in a pandemic like the current COVID-19 pandemic, change of address to more remote places, or even holiday plans.

Clinicians have different concerns to their patients. Issues including the need for patient weight to calculate the dose of LMWH, limited experience with this diagnosis or with prescribing adequate doses of NOAC, and the time requirements for the treatment puts additional pressure on general practitioners. A recent survey in a hospital setting in Qatar found that confidence in prescribing NOAC was very limited[45] which should raise concerns when new pathways are implemented. Othieno et al.[11] showed that LMWH treatment in the community was no worse than hospital treatment, but there is a need to explore further as NOAC are now more commonly used. Furthermore, NOAC are not always prescribed appropriately[46] and attitudes, although explored elsewhere,[12,45] are not necessarily progressing. For clinicians, management plan decisions could also be affected by whether the patient is affected by a high-risk infection like COVID-19 or if the services are limited because of other factors.

The situation is still evolving as the systematic review recently published by Wang et al.,[47] in opposition to the recent Chest guidelines,[36] concluded that NOAC were the first choice for treatment in patients with cancer. NOAC are increasingly replacing previous agents as first choice for the management of VTE.

Strengths and Limitations

The combined approach, assessing what is happening in general practice in England and what are the recommendations on treatment, provided a clear understanding of initial management of DVT in England, showing its variability. However, there is little use of community pathways for the initial treatment of DVT, with many areas heavily dependent on secondary care. Treatment options vary but there is no clear more efficient therapy, nor indication that primary care pathways are better. Confidence and safe prescribing are issues highlighted, and in need of further analysis.

CONCLUSIONS

Primary care is starting to manage DVT initial prescription and to organise tests without the need for patients to attend accident and emergency, as was previous practice. Policies are variable, as are clinicians' expertise and patient options. Implementation of new guidelines in general practice should be more uniform and less dependent on geography, and patients should be given more choice, which would then allow research to produce clearer guidance.

Implications for Research and Practice

There are still knowledge gaps regarding the safety of initial treatment of DVT in the community, as clinicians' choices are based on what is available in their CCG and the expertise on the matter is limited. General practitioners' confidence in prescribing NOAC needs further assessment.

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Concerns Regarding the Management of β-Thalassaemia Patients in the Era of COVID-19

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Abstract

Many cases of pneumonia clustered in the city of Wuhan, China, were reported in December 2019, and source tracing has showed Huanan Seafood Market, Wuhan, China, as the origin. In this work, the authors summarise their concerns for thalassaemia patients, a unique group with several heart, liver, and blood comorbidities.

INTRODUCTION

Thalassaemia (from the Greek word thalassa [sea]) represents a group of genetic haemoglobinopathies that have emerged in certain regions of the world (Sub-Saharan Africa, the Indian subcontinent, Southeast Asia, and the Mediterranean region) where malaria was (or is) endemic. Thalassaemia is the most widely known haemoglobinopathy and several changes in the human immune system have been associated with thalassaemia, including a reduction in neutrophil counts, changes in the number and function of natural killer cells, increase in the number and function of CD8 suppression cells, dysfunction of macrophages, chemotaxis, and phagocytosis, and production of INF-γ.

Ongoing regular transfusions are the mainstay of therapy for patients with β-thalassaemia. During the current COVID-19 pandemic, several concerns have been raised regarding the diagnostics, and particularly the therapeutic approaches, for this specific population.

COVID-19 AND CARDIOVASCULAR DISEASE

The outbreak of the COVID-19 infection has compelled many countries to close the regular outpatient cardiovascular health care units until the pandemic is over. This applies to thalassaemia patients as well, who are typically advised to attend these facilities annually. While the COVID-19 infection rates remain high, it is recommended that thalassaemia patients with

scheduled cardiovascular evaluations are to postpone their medical appointments for at least 3 months. This recommendation is valid for patients with absence of recent symptoms related to cardiovascular disease. Patients with recent onset of symptoms or signs of heart disease should be examined on an emergency basis. As a first step, they should refer to the attending physician who will examine and evaluate the medical condition and suggest whether specialised cardiovascular evaluation is required.

When cardiovascular evaluation is warranted, preventive measures should be applied. The standard precautionary measures include hand washing, use of surgical face masks, and sanitisation of medical equipment after use. Special measures may be applied to high risk patients, such as the use of personal protective equipment including; gowns, headcover, eye protection, shoe covers, and N95 or N99 respirator masks. Medical examination should be focussed on the specific clinical question raised by the referring physician and electrocardiography and transthoracic echo evaluation should only be performed in those cases with clinical indication.

Because of the wide range of cardiovascular clinical manifestation among β-thalassaemia patients, it is difficult to accurately predict possible cardiovascular complications as a result of acute COVID-19 infection. Early data from the general population have shown that pre-existing cardiovascular disease is associated with adverse events.[1] Thus, β-thalassaemia patients with pre-existing left ventricular dysfunction are at the highest risk. In addition, vigilance is required in isolated right ventricular dysfunction as pulmonary infiltration and subsequent hypoxemia may increase the afterload of an impaired right ventricle, resulting in further deterioration of its function. Acute decompensation of the right ventricle may lead to circulatory collapse and increased mortality. Deterioration of pre-existing or new-onset pulmonary hypertension are findings that should be taken into account.

Patients without pre-existing cardiovascular disease are at a lower risk for adverse events in the case of COVID-19 infection. However, early studies have shown that up to 20% of the patients with COVID-19 infection had evidence of myocardial injury, which is defined as increased blood levels of high-sensitivity troponin I or T above the 99th-percentile upper reference limit, irrespective of clinical presentation.[1] The mechanisms responsible for myocardial injury are complex and not well defined, although coronary plaque rupture, direct cardiomyocyte insult, and myocardial oxygen supply/demand mismatch have been proposed. Mild elevation of cardiac biomarkers in the absence of evidence of acute myocardial ischaemia (no related symptoms, absence of electrocardiographic abnormalities, or new echocardiographic findings) is nonspecific and of limited clinical use. On the contrary, significantly elevated cardiac biomarkers, especially when accompanied by related symptoms or evidence from electrocardiography or echocardiography should classify patients at the highest risk, as myocardial injury is associated with increased in-hospital mortality, irrespective of comorbidities.

Special consideration should be given to patients receiving appropriate medical treatment for COVID-19 infection. Current proposed medical treatment consists of a combination of azithromycin and hydroxychloroquine. Both drugs are known for prolongation of the QT interval that predisposes to lethal polymorphic ventricular arrhythmias (torsades de pointes).[2] Risk stratification tools have already been published and should be used in specific patient groups.[3] Previous studies regarding thalassaemia patients have shown that specific electrocardiographic abnormalities are more common among β-thalassaemia patients, with increased corrected QT (QTc) interval duration being among them.[4,5] The combination therapy of azithromycin plus hydroxychloroquine should not be given to patients with a QTc interval >500 milliseconds or congenital long QT syndrome. Patients with moderately increased QTc interval (440–500 milliseconds for men and 460–500 milliseconds for women) should receive the combination therapy as inpatients under monitoring. Patients with a normal baseline QTc interval could receive the combination therapy as outpatients, provided that the QTc interval is measured at 24 hours and 72 hours after treatment initiation. The combination therapy should be withheld if the QTc interval increases >60 milliseconds compared to baseline and if it exceeds 500 milliseconds as an absolute value or syncope occurs. The decision to withdraw one agent or to reduce the dose of the combination therapy should be made on

a case-by-case basis by a team of physicians including infectious disease specialists and cardiologists. Another consideration regarding the proposed use of tocilizumab, an IL-6 receptor monoclonal antibody, as a therapeutic agent in the inflammatory pathway is the reported increase in serum triglycerides.

COVID-19 AND HAEMATOLOGICAL MANIFESTATIONS

In patients who develop sepsis from COVID-19, coagulopathy development is one of the primary and persistent features associated with poor outcomes. Thalassaemic patients have low protein S and protein C levels; increased platelet accumulation; and monocyte, granulocyte, and endothelial cell activation. In most thalassaemic patients, markers of platelet and coagulation activation are persistently elevated, even without significant thromboembolic events. An increase in D-dimers is one of the most common laboratory findings in COVID-19 patients requiring hospitalisation and is not solely attributable to the presence of a thrombus but also a result of the inflammatory response.

The authors noticed the development of disseminated intravascular coagulation on Day 4 in only one surviving patient (0.6%) in the 71.4% of patients who did not survive the infection, compared to disseminated intravascular coagulation. Furthermore, they also noted a statistically significant increase in D-dimer and prothrombin time levels, and a decrease of fibrinogen levels at Days 10 and 14 in nonsurvivors. This demonstrates the considerable importance of daily laboratory monitoring in these patients.[4] The only treatment widely available in patients in this regard is the prophylactic dose of low-molecular-weight heparin, that should be considered in thalassaemic patients but also in other high thrombotic risk haematological disorders in the absence of any comorbidities.

Patients with thalassaemia major progressively develop iron overload. Serum ferritin level is traditionally used for serial testing and some patients with excessive COVID-19 sepsis have laboratory evidence of an increased inflammatory response, comparable to cytokine release syndrome, and persistent fever. Elevated inflammatory markers such as ferritin and elevated proinflammatory cytokines, thrombocytopenia with increased bleeding risk in patients who are receiving anticoagulant, or antiplatelet treatment and lymphopenia have been associated with critical and fatal outcome.[6] Another issue for this specific patient population is blood transfusion. It should be made clear that systematically transfused patients should not delay or postpone their scheduled transfusions despite fear of SARS-CoV-2 infection. Outbreaks of emerging infections negatively affected blood supply, and the prospect of transfusion transmission is worth consideration. Worldwide, most blood centres or blood banks have adopted the following actions during the recent outbreak: 1) taking body temperature prior blood donation, 2) supplementary questions in the donor evaluation questionnaire to determine high-risk donors, 3) recall all blood donors and ask them and their families about their general physical condition following the donation while temporarily not offering the collected blood bag. Lastly, the authors also propose blood donors to be screened using smears or serological tests (anti-SARS-CoV-2 IgG and IgM). They also consider the increased risk of haemolytic crisis in thalassaemic patients with glucose 6-phosphate dehydrogenase deficiency and the need to carry out preventive enzymatic screening tests even for asymptomatic patients before initiating chloroquine or hydroxychloroquine treatment. More than 1,300 clinical trials include drugs and monoclonal antibodies while aiming to evaluate the consequences of COVID-19 infections of patients with haematological diseases.[7] The effect of COVID-19 on bone marrow transplant recipients is unknown, but the authors encourage donors of haematopoietic cells to continue volunteering and further encourage the continuation of gene therapy programmes with all the appropriate COVID-19 precautions.[8]

COVID-19 AND THE LIVER

Based on medical records from hospitalised patients, COVID-19 infection can cause liver injury with increased levels of aspartate aminotransferase and alanine transaminase, and slightly elevated bilirubin in a proportion ranging from 14–53%.

Liver abnormalities occur more frequently in severe COVID-19 cases compared to mild cases.[8] Liver injury in mild COVID-19 cases is transient and does not require specific treatment. Additionally, patients with underlying liver disease may be more susceptible to liver injury but strong data are currently lacking.[9]

The proposed off-label therapeutic agents (azithromycin, chloroquine, remdesivir, and tocilizumab) used in clinical trials to manage severe symptomatic COVID-19 infected patients may be hepatotoxic and close monitoring of liver enzymes is mandatory. The presence of abnormal liver biochemistry is not a contraindication for the use of anti-COVID 19 investigational drugs.[10]

Furthermore, in thalassaemic patients with chronic hepatitis C virus infection the new antivirals (direct-acting antivirals) do not have any drug interaction with chloroquine or azithromycin and, notably, sofosbuvir has been found to exhibit anti-COVID-19 RNA polymerase activity *in vitro*. Furthermore, treatment with direct-acting antivirals may theoretically, in parallel, have a beneficial effect on COVID-19 superinfection but this has yet to be proven.[11]

Patients with hepatocellular carcinoma should continue appropriate imaging surveillance and treatment.

DISCUSSION

In general, there are few to no treatment options for unexpectedly emerging viral diseases. Parallel to this awareness, currently there is no vaccine to effectively treat or to prevent infection with COVID-19. The group of β-thalassaemia patients are a specific population with multisystemic involvement thus several concerns on prophylactic practices have been raised and a more cautious therapeutic approach established to avoid any severe complication of COVID-19 infection.

The authors propose the assessment of common laboratory characteristics such as lymphopenia, liver enzymes, lactic dehydrogenases inflammatory markers (e.g., C-reactive protein, and ferritin), prothrombin time, troponin, creatine phosphokinase, renal injury markers, etc. and monitoring for any changes in carriers or asymptomatic patients. For suspected patients, chest X-ray and electrocardiograms are also considered.

To avoid the spread of the virus to other patients, transfusions should be performed in a dedicated isolation zone. Patients should be encouraged to receive medical treatment, communicate with their doctors, and seek psychological support during the pandemic. Chloroquine has been well established with *in vitro* effects on uncoating inhibition and/or post-translation modifications of newly synthesised proteins, especially glycosylation inhibition in many viruses, including HIV. Recent studies have shown that remdesivir and chloroquine are highly successful in suppressing the coronavirus *in vitro*.

Both *in vitro* and human-based SARS-CoV and MERS-CoV trial molecules are being tested for COVID-19. Studies evaluating antiviral activity of Type I and Type II interferons (IFN) revealed that IFN-β is the most potent IFN and limited *in vitro* replication of MERS-CoV.

According to a South Korean human MERS-CoV research study, the use of a combination of lopinavir/ritonavir (anti-HIV drugs), EJMO 5 pegylated IFN, and ribavirin has so far been efficient in viral clearance.[11,12]

CONCLUSION

Since patients with β-thalassaemia are considered a risk population for COVID-19 infection, measures such as effective dissemination of disease information on the elimination of the source of infection, early detection, monitoring, isolation, supportive care and the avoidance of needless panic should be taken. Centers for Disease Control and Prevention (CDC) encourage individuals to follow simple precautions such as hand washing and sanitisation, using disinfectant solutions, and avoiding contact with patients to prevent droplet spread of viruses.

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Expanding the Role of CAR-T Cell Therapy to Systemic Lupus Erythematosus

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Abstract

Systemic lupus erythematosus (SLE) is a chronic inflammatory autoimmune disorder resulting from autoantibodies produced by B-cell derived plasma cells. Clinical presentation ranges from mild skin rash to multiorgan failure. Regardless of the clinical presentation or severity of the disease, patients with SLE often require life-long treatment. Current treatment recommendations for SLE include hydroxychloroquine, glucocorticoids, immunomodulatory agents, cyclophosphamide, and biologic agents. Despite availability of these agents, the condition of some patients with SLE progressively worsens. With limited treatment options, new and novel therapeutic approaches are needed. Given the active role of B cells in the pathophysiology of SLE, they present an attractive target for therapies evolving in the oncology field. Amongst these, immune effector cell therapies, including chimeric antigen receptor (CAR)-T cell therapy, have proven beneficial in targeting B cells. The eradication of B cells, along with the potential for T cell persistence, has resulted in prolonged remission or stable disease. This review provides an overview of the pathophysiology of SLE; current treatment options, including monoclonal antibodies targeting cluster of differentiation-20 (CD20), CD22, and B cell-activating factor (BAFF); and explores why and how immune effector cell therapies may prove a promising therapeutic option for this patient population, particularly for individuals with refractory disease. Clinical implications from currently approved U.S. Food and Drug Administration (FDA) agents for haematologic malignancies are discussed and provide insight into considerations for applying this therapy to the patient population with SLE in the context of clinical trials.

INTRODUCTION

Systemic lupus erythematosus (SLE) is a chronic autoimmune disease with unknown cause and varying clinical presentation, ranging from mild rash to multiorgan failure. SLE predominantly affects females, particularly those of childbearing age. The prevalence is higher in individuals belonging to African American, Asian, or Hispanic ethnic groups compared to those of Caucasian ethnicity.[1] The pathogenesis of SLE often involves production of immunogenic forms of DNA, nuclear proteins, and other self-antigens.[2] These immunogenic

materials provoke the immune system, leading to activation of T cells and B cells and subsequently producing autoantibodies and pathogenic effector cells, such as Th1 and Th17.[3] As a consequence, immune complexes between autoantibodies and their cognate antigens are formed and deposited in various tissues causing complement activations. These activated Th1/Th17 cells produce and secrete cytokines and chemokines causing chronic inflammation. If left unchecked, these can lead to severe organ damage and have life-threatening consequences (Figure 1).

Therapeutic options for the management of SLE have evolved from antimalarial agents such as mepacrine and hydroxychloroquine in the 1950s to immunosuppressive agents including methotrexate, azathioprine, and tacrolimus in the 1960s.[4] More recent advances have included the use of targeted therapies such as rituximab, followed by the U.S. Food and Drug Administration (FDA) approval of belimumab, a humanised monoclonal antibody, in 2011.[4] Despite availability of these advanced opportunities, it remains essential to explore additional therapeutic options, particularly for individuals with severe presentation of refractory disease. New and novel therapies in the oncology field, specifically immune effector cell therapies, are an attractive option for clinical trials in the patient population with SLE based on their capacity to target specific surface antigens, as well as the potential for persistence which may convey extended therapeutic benefit. This review provides relevant information that could potentially lead to a drug repositioning investigation of chimeric antigen receptor (CAR)-T cell therapies for severe and refractory SLE.

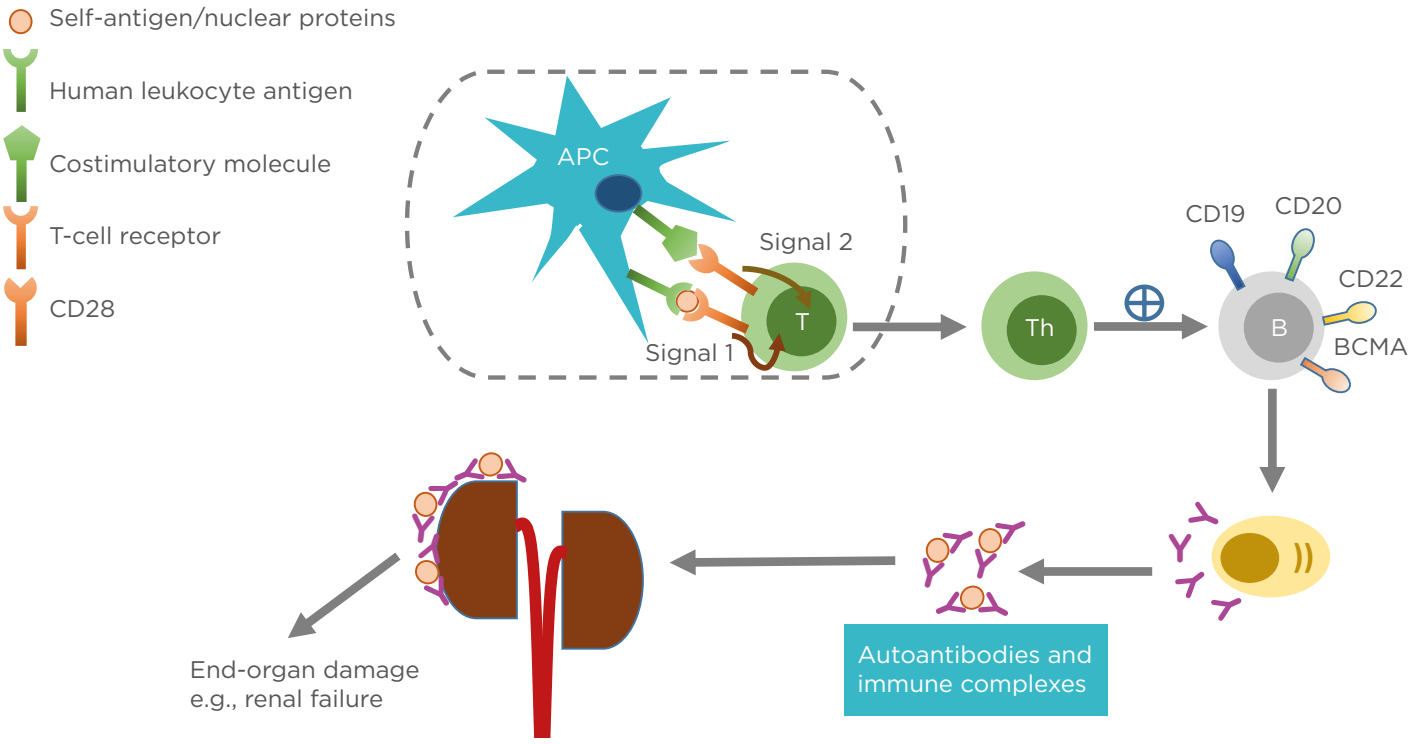

Figure 1: Pathophysiology of systemic lupus erythematosus.

Antigen-presenting cells, such as dendritic cells, uptake self-peptides or nuclear proteins and migrate to draining lymph nodes where they become mature. The mature dendritic cells interact and engage with and activate naïve T cells in the lymph nodes through Signal 1 (human leukocyte antigen: autoantigen complex–TCR interaction) and Signal 2 (co-stimulatory molecule–CD28 interaction). Activated T cells become effector cells i.e., T-helper cells and cytotoxic T-lymphocytes (not shown). The effector cells promote B-cell differentiation into autoantibody-producing plasma cells. Consequently, immune complexes are formed. Deposition of immune complexes at various tissues including the kidneys lead to end-organ damage.

APC: antigen-presenting cell; B: B cell; BCMA: B-cell maturation antigen; CD: cluster of differentiation; T: T cell; Th: T helper cell.

ROLE OF B CELL DEPLETION IN SYSTEMIC LUPUS ERYTHEMATOSUS

B cells are involved in crucial processes of SLE development. The role of B cells in the pathogenesis of SLE includes antigen presentation, T-cell activation, and autoantibody production.[5] Depletion of B cells, therefore, is an attractive target for treatment of SLE. In the past decade, there have been several trials designed specifically to address such treatment interventions.[6–9] Strategies developed to deplete B cells focussed on identifying targets pertaining to B lineage cells, which include cluster of differentiation-19 (CD19), CD20, CD22, and B cell-activating factor (BAFF).

CD19 is a transmembrane glycoprotein found on B lineage cells, spanning from pre-B cells to plasma cells.[10] It is required for normal B cell development and antibody production.[11,12] CD19 protein forms a complex with CD21, CD81, and CD225 in the membrane of mature B cells. Together with the B cell antigen receptor, this complex signals the B cell to decrease its threshold for activation by the antigen.[13] Thus, CD19 is considered a co-stimulatory molecule for B cell receptor signalling. Deficiency in CD19 expression on B cells leads to hypogammaglobulinaemia.[11] Among individuals with SLE, $CD19^+$ B cells are associated with SLE activity, exhibiting elevations in the presence of active versus stable disease. Further, programmed death ligand-1 (PD-L1) has higher expression in patients with SLE compared to healthy controls, and this expression is higher still in patients with active versus stable disease, suggesting a role of PD-L1 in the regulatory mechanisms of B cells.[14] Given the activity of CD 19^+ B cells with and without PD-L1 expression, they may serve as a therapeutic target in SLE management. There are currently two targeted agents which could potentially be applied as SLE therapy: obexelimab, which targets CD19 and Fcγ receptor IIB (FcγRIIb);[15] and CD19-directed CAR, of which there are two currently FDA-approved agents with indication in B cell malignancies. Tisagenlecleucel is indicated for treatment of relapsed or refractory acute lymphoblastic leukaemia and diffuse large B cell lymphoma (DLBCL)[16] and axicabtagene ciloleucel is indicated for treatment of relapsed or refractory large B cell lymphoma, including DLBCL, primary mediastinal B cell lymphoma, high grade B cell lymphoma, and DLBCL arising from follicular lymphoma.[17]

In addition to CD19, other targets for B-cell depletion may include BAFF, CD20, and CD22. CD20 is expressed on all mature B cells including memory B cells and plasma cells. Its function involves B cell differentiation, activation, and proliferation.[10] Rituximab, a chimeric monoclonal antibody against CD20 approved for treatment of chronic lymphocytic leukaemia and non-Hodgkin's lymphoma, efficiently eliminates the majority of B lineage cells; however, it may not deplete the whole memory B cell compartment, leading to disease relapse.[18] As a result, clinical outcomes of rituximab in SLE are rather poor.[7,8] In addition, rituximab requires repeated administration to achieve and maintain a therapeutic dose. Newer anti-CD20 monoclonal antibodies[10] such as obinutuzumab, ofatumumab, veltuzumab, and ocrelizumab, are viable options for SLE, one of which is currently under clinical investigation.[19] Another trial studied outcomes of participants with nephrotic syndrome treated with ocrelizumab,[20] in which participants without nephrotic syndrome achieved renal response at twice the rate of those with nephrotic syndrome who were treated with ocrelizumab.[21] CD22 (also known as Siglec-2), a member of the sialic acid-binding immunoglobulin-like lectins family, serves as an adhesion molecule. It has been shown that blockage of CD22 affects B cell migration in SLE.[22] However, epratuzumab, an investigational anti-CD22 monoclonal antibody, did not result in improvements when used in combination with standard therapies for moderate or severely active SLE.[9] Lastly, BAFF, also known as B lymphocyte stimulator, is an activating factor for B cell survival and function. Binding of the homotrimer BAFF to the BAFF receptor on naïve and memory B cells enhances B cell survival.[23] High levels of soluble BAFF are detected in individuals with autoimmune diseases including SLE,[24] making BAFF an attractive target for SLE management. Belimumab is a monoclonal antibody that neutralises BAFF, currently approved for treatment of SLE when used in combination with standard therapies. Unlike monoclonal antibody drugs, CAR-T cells appear to last longer in the systemic circulation, which may extend the period of disease remission.

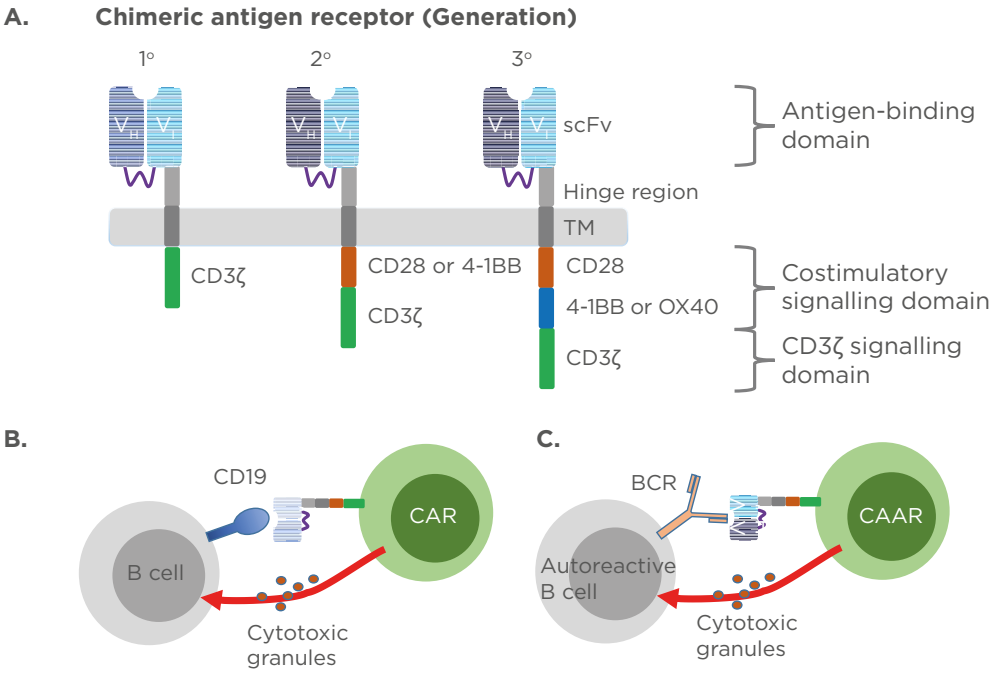

Figure 2: Chimeric antigen receptor constructs and their mechanism of action.

(A) Three generations of chimeric antigen receptors. First-generation CAR are composed of extracellular scFv that are specific to the antigen, transmembrane domain, and cytoplasmic signalling domain CD3ζ. Second-generation CAR incorporate a co-stimulatory domain i.e., CD28 or 4-1BB into the cytoplasmic tail in addition to CD3ζ. Third-generation CAR incorporate two co-stimulatory domains such as CD28 and 4-1BB or OX40. CD19-targeted CAR-T cells (B) or chimeric autoantigen receptor-T cells (C) are genetically engineered to specifically eliminate autoreactive B cells. Direct interaction between CAR-T cells and CD19 expressing B cells or CAAR-T cells and autoreactive B cells expressing B cell receptor recognising autoantigen leads to activation of the CAR/CAAR-T cells to release cytotoxic granules and destroy their targets.

BCR: B cell receptor; CAR: chimeric antigen receptors; CAAR: chimeric autoantigen receptor; scFv: single-chain antibody variable fragment; TM: transmembrane domain.

TARGETING AUTOREACTIVE B-CELLS IN SYSTEMIC LUPUS ERYTHEMATOSUS WITH CAR-T CELLS

The chimeric antigen receptors combine antigen binding domains and signalling domains to facilitate a targeted, receptor-driven response (Figure 2).

The success of CAR-T cell therapies in the context of B cell malignancies has led to the exploration of their application to autoimmune conditions, including SLE.[25,26] These hypotheses have begun to be evaluated in both murine and human research.[27,28] Murine models suggest the potential of CAR-T cells as a potential treatment for SLE, with results showing extended survival and sparing of target organs.[27] In these models, purified $CD8^+$ T cells were utilised in place of autoreactive $CD4^+$ T-helper cells, given the potential risk for a disease-enhancing effect in SLE. One study is evaluating the safety and efficacy of CAR-T cells for the treatment of SLE.[29] The greatest potential challenge in the application of these therapies to autoimmune conditions is the scarcity of tissue-specific antigens to which the CAR can bind to exert a therapeutic effect.[30]

In addition, it is hypothesised that the chimeric immune receptors, such as CAR and B cell antigen receptors expressed by T regulatory lymphocytes (Tregs), upon binding with specific T cell conjugates, result in the direct protection of normal cells.[30] Among the working hypothesis for the potential role of CAR-T cell therapy is the potential for generating Tregs,

which occur at lower frequency in SLE and lead to immune dysfunction. The application of CAR to bind extracellular antigen recognition domains and intracellular hinge domains may be exploited to activate and proliferate Tregs, protecting tissues from a T-lymphocyte attack. There are two mechanisms for expanding Tregs, one involving the use of *ex vivo* expansion using anti-CD3 or CD28 antibodies, the other involving conversion of conventional T cells to Tregs through the use of transforming growth factor-β alone or in combination with all-trans retinoic acid, rapamycin, or rapamycin alone.[31] Once expanded, the CAR engineered Tregs may suppress immune response through several mechanisms including inhibition of antigen-presenting cells, interference with lymphocyte metabolism, secretion of anti-inflammatory cytokines, induction of apoptosis, and cell-to-cell interaction, each of which has the potential to mitigate autoimmune response[31] and result in reduced tissue damage. Similarly, studies have demonstrated the capacity of B cell antigen receptor-Tregs to indirectly disrupt B cell function through the suppression of T effector cells.[30] It is therefore hypothesised that chimeric autoantibody receptor (CAAR), a chimeric receptor that is designed to express a specific autoantigen, could be used therapeutically for autoantibody-mediated autoimmune diseases, including SLE.[30] In addition to their activity against autoreactive B cells, CAAR products may produce persistence and resulting memory cells with potential for reduced off-target toxicity whilst devoid of B cell aplasia and hypogammaglobulinaemia (Figure 2).[30]

ANTICIPATORY ADVERSE EFFECTS OF CAR-T CELL THERAPIES IN SYSTEMIC LUPUS ERYTHEMATOSUS

Systematic reviews of commercially available CAR-T cell therapies highlight toxicities including cytokine release syndrome (CRS), neurotoxicity, and B cell aplasia.[32] CRS is an inflammatory response observed in >70% of patients receiving CAR-T cell therapy and results in fever, hypotension, capillary leak syndrome, and potential for coagulopathies and multiorgan failure.[33] CRS most often occurs 1–6 days following infusion, with 95% of cases occurring within the first 12 days post-infusion, though late onset CRS has been observed.[34] CRS is also a potential complication associated with the accumulation of transforming growth factor-ß when applied to the autoimmune population.[30] CRS is successfully managed with tocilizumab, an IL-6 receptor antagonist. Tocilizumab is a recombinant humanised anti-human IL-6 receptor IgG1k monoclonal antibody and is approved for patients with CAR-T cell-induced severe or life-threatening CRS.[35] The Risk Evaluation and Mitigation Strategy (REMS) programme is instituted for both tisagenlecleucel and axicabtagene ciloleucel, as well as tocilizumab, which is a crucial component of the REMS programme.

Immune effector cell-associated neurotoxicity syndrome is believed to be related to fever, high serum IL-6, and high monocyte chemoattractant protein-1 concentrations, and typically occurs within 4–5 days of infusion.[36] Symptoms include delirium, headache, and expressive aphasia, with more serious presentations of cerebral oedema and brainstem haemorrhage.[36] Management focusses on symptoms and may include corticosteroids to reduce inflammation, levetiracetam as prophylaxis for seizures, and possible use of siltuximab for CRS-related neurotoxicity.

Late effects of CAR-T cell therapy have also been observed. Hypergammaglobulinaemia has been reported, resulting in decreased antibody production with resulting low IgG levels approximately 9 weeks following CAR-T cell infusion and potential persistence for ≥4 years following treatment.[37,38] Treatment involves IgG replacement every 3-4 weeks and as needed to maintain therapeutic IgG levels. Monitoring laboratory values to identify critically low IgG is pivotal because of increased risk for infection. B cell aplasia is considered an on-target, off-tumour effect of therapy, resulting in acute and chronic B-cell targeting by CAR-T cells which have demonstrated persistence.[39] This persistence, while contributing to B cell aplasia, is also believed to be associated with continued immunosurveillance for malignant cells, thereby resulting in sustained remissions.[40]

Understanding the known toxicities of therapy is important when considering how such therapies may be applied to the patient population with SLE. Like the current toxicities

observed in commercial application of CAR-T cells to haematologic malignancies, CAR products may contribute to cytokine release and on-target toxicities, such as B cell aplasia.[32] When applied to patient populations who are autoimmune, the possibility of nonspecific immune suppression may contribute to increased risk of infection or the possibility of undetected tumour growth.[31] Newer generation CAR products are demonstrating fewer toxicities in clinical trials.[41] Further studies are needed to evaluate the underlying pathophysiologic mechanisms and how these are operationalised when CAR treatment is applied to human subjects with SLE. As these next generation CAR are being applied to a broadening population of patients with haematologic and solid tumour malignancies,[42] there is promise for expanding the application of CAR-T cell therapy beyond oncology, with immune-related conditions an optimal therapeutic area.

POTENTIAL SPACE FOR CAR-T CELL THERAPIES IN SYSTEMIC LUPUS ERYTHEMATOSUS

The therapeutic approach and patient populations who are autoimmune, to which CAR-T cell therapies (tisagenlecleucel and axicabtagene ciloleucel) may be safely and successfully applied, has yet to be determined. Given the lack of a current curative option for SLE, consideration might be given to the application of CAR-T cell therapies following trials establishing the safety and efficacy of this approach in humans. Key insights from commercial CAR-T cell therapy approvals suggest that, as well as patients receiving this therapy for oncologic malignancies, individuals with autoimmune conditions might also undergo this treatment. Successes in CD19 directed CAR-T cell therapies in B cell lymphomas have shed some light on CAR-T cell products as a potential treatment modality for severe SLE, including renal (lupus nephritis) and extrarenal disease. Given the current focus of CAR-T cell therapy on CD19 directed B cell malignancies, the same application in SLE may provide an initial target, as is currently being evaluated in a clinical trial (NCT03030976).[28] Other potential targets, each of which contributes to T cell proliferation, include the CD3 complex, phosphoinositide-3 kinases, CD44, and IL-2.[43]

While currently approved CAR-T cell products may have some application for the patient population with SLE, critical questions remain to be answered. First, will this therapy demonstrate therapeutic benefit for this patient population and if so, which products are suitable for which patients with SLE? Data from pharmacological study of second-generation CAR indicates that CD28-based CAR exhibit rapid expansion and boost effector functions, whereas constructs with 4-1BB generate greater persistence and longevity.[44] Whether these observations contribute to product selection based on patient characteristics remains to be seen. Experience with tisagenlecleucel and axicabtagene ciloleucel provide insight into clinical applications if and when such therapies are applied to treat SLE; however, a clinical trial is warranted.[27]

CAAR as opposed to CAR derived products may be most beneficial, given the targeting of autoantibody cells that underlie the pathophysiologic mechanisms of SLE (Figure 2). The broader classification of immune effector cells; genetically modified cells from diverse lineages, including T cells, macrophages, and dendritic cells; and natural killer cells offer unique opportunities to explore various therapeutic targets in the highly heterogeneous SLE presentation.[45] Further studies are needed to apply both commercially available and investigational effector cell therapies to the SLE populations to identify which products are most effective in producing a durable response.

CONCLUSION

SLE is an autoimmune disease that can progress to end-organ damage. Standard treatments for SLE may be adequate to control the disease for some patients. Unfortunately, many SLE patients continue to progressively worsen and are refractory to standard of care, requiring novel treatment modalities. Recent approaches include depressing circulating B cells with rituximab, obinutuzumab, ocrelizumab, or belimumab. The efficacy of CD19 directed CAR-T cell therapies in B cell lymphomas may serve as a potential treatment modality

for SLE. If results in the SLE population mirror those in individuals with haematologic malignancies, such approaches may require a single treatment that can produce cellular persistence resulting in longitudinal disease control, whilst acknowledging acute and long-term toxicities including CRS, immune effector cell-associated neurotoxicity syndrome, or B cell aplasia. Nonetheless, immune effector cell therapies, including but not limited to CAR-T cell therapies, provide a novel option for evaluating the effect of such therapies on SLE disease response, survival, and quality of life in the context of clinical trials.

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Pancytopenia Secondary to Adult Osteopetrosis

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Abstract

Osteopetrosis (OP) is a rare genetically metabolic bone disorder caused by severe impairment of osteoclast-mediated bone resorption. It is characterised by extensive sclerosis of the skeleton, fragility fracture, haematopoietic insufficiency, nerve entrapment syndromes, and growth impairment. It is clinically classified into two major types: infantile (autosomal recessive, malignant) and adult (autosomal dominant, benign) OP. The infantile type is usually diagnosed early in life, while adult type is diagnosed in late adolescence or adulthood. Approximately one-half of patients are asymptomatic and the diagnosis is made incidentally. However, some patients might present with one or more complications of OP, and the diagnosis is made during the work-up and evaluation. Here, the authors describe an unusual case of adult type OP presented with pancytopenia.

CASE PRESENTATION

The 35-year-old female of Arab ethnicity was admitted to the Department of General Internal Medicine in King Saud Medical City, Riyadh, Saudi Arabia, with a long history of approximately 7 years of intermittent lethargy, dizziness, and exertional dyspnoea. She sought different healthcare centres, where she received multiple blood transfusions, intravenous iron infusion, and vitamins. She gave a history of similar condition to her elder sister, who had passed away. There was no history of bleeding, abnormal menstrual cycle, bony fracture, or haematological disease. On examination, she was fully conscious, alert, and oriented to time, place, and person, with no skeletal deformity. The patient was found to be moderately pale. She had palpable spleen 2 cm below the left subcostal margin in its axis with palpable liver 3 cm below the right subcostal margin, nontender, smooth-surfaced, and soft in consistency. Neurological and ophthalmological examinations were both normal.

Laboratory examination yielded a red blood cell count 1.44 cells/mm^3, haemoglobin 4.80 g/dL, mean corpuscular volume 107.60 fL, mean corpuscular haemoglobin 33.30 pg, red blood cell distribution width 17.70%, reticulocyte count 1.51%, white blood cell counts 2.89 cells/mm^3, and platelet count 188.00 /mm^3. Peripheral blood smear revealed marked macrocytic anaemia, polychromasia, few teardrop cells, mild leukopenia, and mild thrombocytopenia. Biochemical analysis was normal, including 195

U/L lactate dehydrogenase, total bilirubin level of 9.3 umol/L, and normal serum calcium and phosphorus levels, with the exception of alkaline phosphatase which was 180 U/L. There was a normal iron profile, except for high ferritin which was 631 ng/mL. Thyroid and parathyroid functions were both normal. Serology for cytomegalovirus, Epstein–Barr virus, viral hepatitis, and HIV was negative. The antinuclear antibody titer was nonsignificant, antidouble stranded DNA was negative, and C3 and C4 were both within the normal reference range. Bone marrow aspiration and touch print showed severe hypocellular diluted bone marrow with cellularity <20%. Bone marrow biopsy and microscopic examination showed entirely thick trabecular bone, filling the whole biopsy with marble-shaped bone and no evidence of malignancy. Skeletal survey and radiological evaluation revealed diffuse bone sclerosis (Figure 1). Posteroanterior chest X-ray showed mild cardiomegaly and a homogeneous increase in bone density throughout the clavicular bones, thoracic cage, and vertebrae (Figure 1A). A noncontrast CT scan showed diffuse increased bone density in the vertebral bodies and ribs with severe osseous sclerosis (Figure 1B). Dual-energy X-ray absorptiometry showed generalised increased bone mineral density. The T-score and the age matched Z-score were very high compared to the expected range for the patient's age according to the International Society of Clinical Densitometry (ISCD) recommendation,[1] in keeping with diffuse dense sclerosis noted in previous CT scans (Figure 2).

Based on the clinical, haematological, radiological, and bone marrow biopsy findings, a final diagnosis of adult-type osteopetrosis (OP) was made. Genetic studies could not be performed. The patient was referred to a specialised centre for bone marrow transplantation where the diagnosis of OP was confirmed. The treating physicians could not find a human leukocyte antigen matching donor in the patient's family; therefore, the patient was started on corticosteroids as a supportive treatment with regular visits to a haematology outpatient clinic for follow-up clinical and laboratory testing.

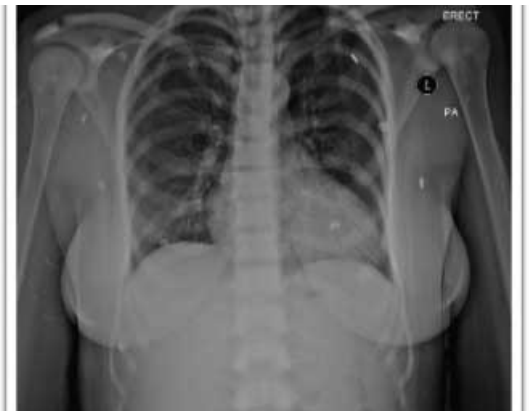
DISCUSSION

OP refers to a group of disorders caused by the severe impairment of osteoclast-mediated bone resorption. As a consequence, bone modelling and remodelling are impaired. The defect in bone turnover characteristically results in skeletal fragility despite increased bone mass, and it may also cause haematopoietic insufficiency, nerve entrapment syndromes, and growth impairment. It is clinically classified into infantile, which is autosomal recessive, malignant, and has a poor prognosis; adult, which is autosomal dominant, benign, and has a good prognosis; and intermediate, which is rare, autosomal recessive, and has a poor prognosis.[2] OP tarda, the benign adult form, is inherited as an autosomal dominant trait. Patients are typically asymptomatic and have good long-term survival rates because bone marrow failure rarely occurs.[3] It is usually detected by a family history of bone disease or as an incidental radiologic finding, and is asymptomatic in approximately 50% of cases. Close to 40% of patients present with fractures related to brittle osteopetrotic bones or with osteomyelitis, especially of the mandible. There is sufficient retention of marrow cavity for normal haematopoiesis to occur in patients with OP tarda. In some cases, there is an elevated acid phosphatase level. Although patients with OP tarda have an increased susceptibility to fractures, healing appears to proceed normally.[4]

OP is characterised by abnormal bone tissue which infiltrates the marrow cavity, resulting in pancytopenia and bone marrow failure. As a compensatory mechanism, extramedullary haematopoiesis occurs in the spleen and/or liver. Clinical features include recurrent fractures, stunted growth, failure to thrive, blindness and deafness from cranial nerve entrapment, and recurrent infections from impaired immune function. These severe clinical features of OP are more common in infantile than adult OP.[5]

In this case, severe pancytopenia was the patient's main presentation with a long history of the symptoms of anaemia and multiple blood transfusions, which is an unusual presentation of adult OP. Moreover, there was no previous history of bony fracture. One of the patient's elder sisters had similar symptoms, but she died with no clear diagnosis and no family history of OP.

A



B

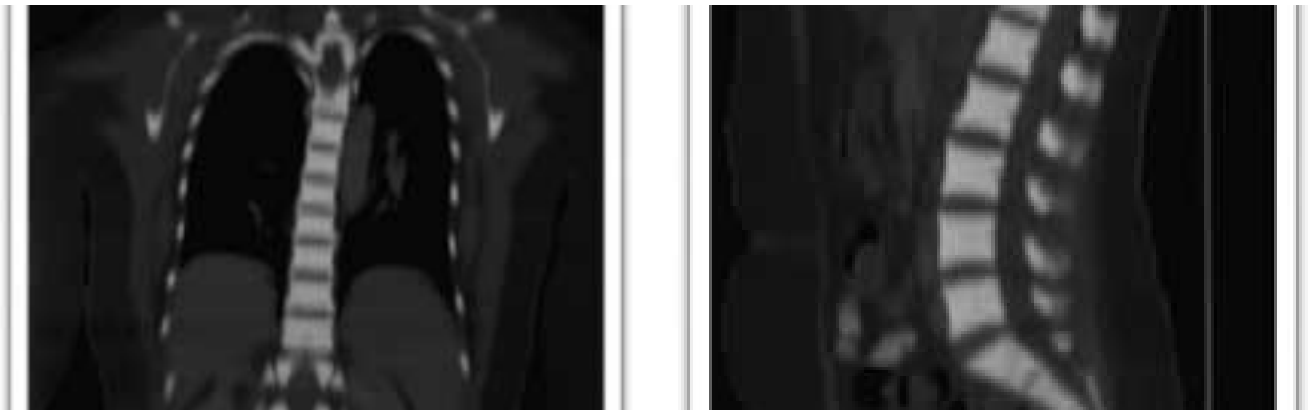
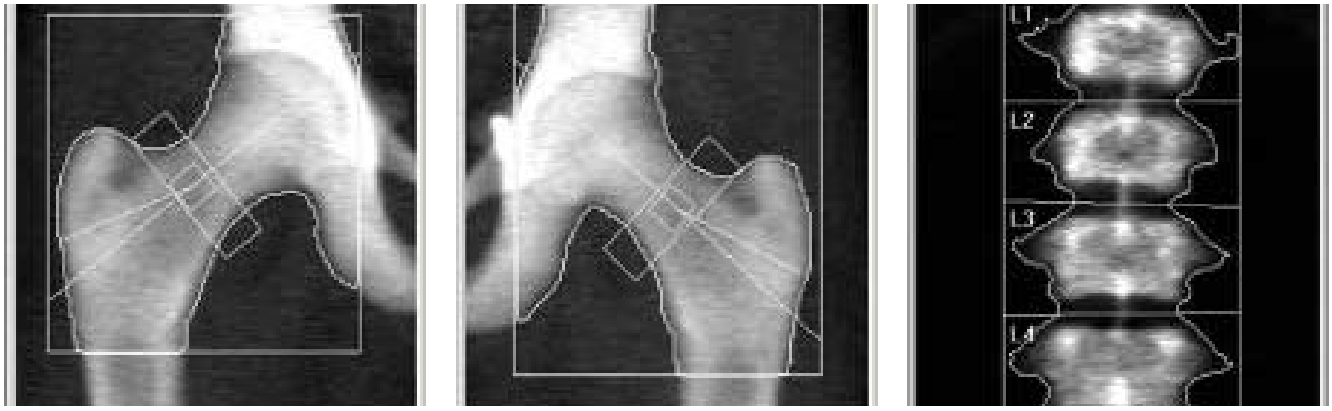


Figure 1: A) Posteroanterior chest X-ray shows mild cardiomegaly and homogeneous increase in bone density throughout the clavicular bones, thoracic cage, and vertebrae. B) Noncontrast CT scan shows diffuse increased bone density in the vertebral bodies and ribs with severe osseous sclerosis

A



B

Region	T-Score (SD)	Comment
Right femur	3.7 (Z-score = 3.9)	Higher than expected range for age
Left femur	3.6 (Z-score = 3.7)	Higher than expected range for age
Lumbar spine	7.2 (Z-score = 7.3)	Higher than expected range for age

Figure 2: A) Dual-energy X-ray absorptiometry scan using both hips and lumbar spine as standard protocol. B) Dual-energy X-rays Absorptiometry shows generalised increased bone mineral density, and the T-score and the age matched Z-score are very high compared to the expected range for age according to the international Society of Clinical Densitometry (ISCD) recommendations, in keeping with diffuse dense sclerosis noted in previous CT scans.

SD: standard deviation.

She also had hepatosplenomegaly upon palpation, which is likely because of bone expansion leading to bone marrow narrowing and extramedullary haematopoiesis.

The diagnosis of OP largely depends on the radiologic features of the skeleton. The presence of bone sclerosis is usually diagnostic of OP. Two types of adult OP are mostly identified based on the distribution of bone sclerosis. Typing the patient's disease helps to predict a fracture pattern because of the nature of the different types. In Type I, sclerosis of the skull mainly affects the vault and the spine does not show much sclerosis. Type II tends to increase the risk of fracture, and sclerosis is mainly found in the base of the skull, the spine always has the rugger jersey appearance, and the pelvis always shows subcristal sclerosis. Transverse banding of metaphysis is common in patients with Type II disease but not in patients with Type I. This finding confirms Type II disease, but its absence does not necessarily indicate Type I.[2]

Some controversy surrounds the role of bone marrow biopsy in the diagnosis of OP; however, the histopathologic studies of the biopsy may be useful to predict the likelihood of bone marrow transplant success. Patients with crowded bone marrow are less likely than others to respond to a transplant. For this patient, the diagnosis of OP was established based on the radiological evidence of dense sclerosis, and bone marrow biopsy was performed to confirm its diagnosis and rule out other causes of pancytopenia.

Genetic studies could not be performed for the patient. A defect in chloride channel 7 α subunit (CLCN7) has been identified in some cases of infantile and adult OP. Most individuals diagnosed with autosomal dominant *CLCN7*-related OP have an affected parent. The proportion of cases caused by *de novo* pathogenic variants is unknown. Each child of an individual with autosomal dominant *CLCN7*-related OP has a 50% chance of inheriting the pathogenic variant.[6]

The treatment of OP depends on its variety and presence of complications. Most cases of adult OP require no specific treatment by itself. This patient, however, had severe pancytopenia, and therefore was referred to a specialised centre for haematopoietic stem cell transplantation, of which might be the only treatment that can provide a cure in such patients. IFNγ1b treatment has been tried in patients with OP and has been reported to result in improved immune function, increased bone resorption, and increased bone marrow space.[7-9] At the time of the study, there was insufficient evidence to support the routine use of corticosteroids in OP.[10]

CONCLUSION/TAKE-HOME MESSAGES

The take-home message of this case is to maintain a high index of clinical suspicion for unusual presentation of adult-onset OP. Therefore, proper clinical assessment and radiographic investigations are essential for diagnosis of OP. Thus, it is important for physicians to be familiar with various clinical manifestations of OP and its radiological features.

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Adult-Onset Still's Disease Complicated with Haemophagocytic Lymphohistiocytosis (HLH): A Case Report

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Abstract

Haemophagocytic lymphohistiocytosis (HLH) is a rare but potentially aggressive and life-threatening syndrome of overactive histiocytes and lymphocytes that commonly affects infants; it is also observed in children and adults of all ages. The disease is differentiated into either primary or secondary causes. Primary HLH tends to be of genetic origin, while secondary HLH results from either infection, autoimmune disorders, or malignancies. Secondary HLH is most commonly associated with viral infections in immunocompromised patients. This paper presents a case of HLH in a tertiary care hospital, associated with adult-onset Still's disease, diagnosed on both biochemical criteria and histopathologic examination of bone marrow smear.

INTRODUCTION

The term haemophagocytic lymphohistiocytosis (HLH) was first described by Farquhar and Claireaux in 1952, who termed the disease familial haemophagocytic reticulosis and presented it as a rare familial disorder characterised by proliferation of histiocytes in solid organs and phagocytosis of blood cells.[1] The pathophysiology and aetiology of HLH involve excessive inflammation and tissue destruction due to abnormal immune activation which is caused by the absence of normal downregulation of activated macrophages, natural killer (NK) cells, and cytotoxic lymphocytes. The most common infectious trigger is a viral infection, especially

the Epstein–Barr virus (EBV). The worldwide incidence of HLH is reported to be 1.2 cases per million persons per year.

CASE PRESENTATION

A 29-year-old Asian male with no known comorbidities presented with complaints of fever (documented up to 104 °C), sore throat, skin rash, yellowish discolouration of eyes and sclera, and generalised abdominal pain for 1 month. The patient had symptoms of generalised weakness, decreased appetite, and clinically significant weight loss. He denied loose motions, easy bruising, blood in vomitus, blood in the stool, pale stools, dark urine, transfusion history, itching, a history of jaundice in his family, intravenous drug abuse, or any recent history of travelling. He was started empirically with intravenous ciprofloxacin, intravenous hydration with 0.9% normal saline, and ibuprofen for his fever, jaundice, and generalised abdominal pain.

The physical examination was unremarkable except for severe pallor; jaundice; two subcutaneous, fluctuant, hyperpigmented nodules to the right of the umbilicus; hepatomegaly; splenomegaly; and cervico-axillary lymphadenopathy. The laboratory findings revealed a haemoglobin of 6.60 g/dL, mean cell volume of 74 fL, total leucocyte count of 18.1×10^9 cells/L, and platelets of 57.0×10^9 /L. The patient had an international normalised ratio of 2.28, serum total bilirubin of 6.23 mg/dL with direct bilirubin of 5.40 mg/dL, alanine aminotransferase of 479 U/L, aspartate aminotransferase of 247 U/L, alkaline phosphatase of 799 U/L, and g-glutamyl transferase of 235 U/L. The differential considerations at this point included acute hepatitis, autoimmune hepatitis, adult-onset Still's disease, polyarteritis nodosa, and cytokine storm secondary to COVID-19.

Further workup showed negative viral serologies, ferritin of 40,000 ng/mL, erythrocyte sedimentation rate of 45 mm/hour, C-reactive protein of 93 mg/L, serum lactate dehydrogenase of 1470 U/L, fibrinogen of 0.57 g/L, serum albumin of 3.26 g/dL, and triglycerides of 234 mg/dL. The peripheral smear showed microcytic, hypochromic anaemia with positive pencil cells and right-sided neutrophil shift. Procalcitonin was within a normal range and blood culture was negative. An ultrasound of his abdomen showed hepato- and splenomegaly (17 cm and 19 cm respectively). All other investigations were unremarkable. An autoimmune profile was negative with normal complement levels. The patient fulfilled Yamaguchi criteria of adult-onset Still's disease,[2] including high spiking fever, evanescent rash, sore throat, hepatosplenomegaly, leukocytosis, elevated polymorphonuclear neutrophil count, high erythrocyte sedimentation rate, high serum ferritin, and elevated liver enzymes, with negative tests for antinuclear antibody and rheumatoid factor (IgM). Confirmatory tests for *Yersinia enterocolitica* and *Mycoplasma pneumoniae* infections were negative, which are considered possible causes of Still's disease. CT scan with contrast showed mildly prominent abdominal wall vessels suggestive of vasculitis, along with axillary and cervical lymphadenopathy and splenomegaly (Figure 1). Histology of the hyperpigmented abdominal nodules following punch biopsy showed leukocytoclastic vasculitis.

Bone marrow aspirate was performed which showed macrophages with classic haemophagocytic activity suggestive of HLH (Figure 2). According to the HLH-2004 protocol,[3] this patient fulfilled six features out of the eight-point diagnostic criteria for HLH, including a persistent fever, bicytopenia, hepatosplenomegaly on an ultrasound of the abdomen, low fibrinogen levels, raised ferritin levels, elevated triglycerides, and histiocytic activity on a bone marrow aspirate (Table 1). In this case, the underlying cause of HLH was suspected to be adult-onset Still's disease. The patient was given high-dose corticosteroids as a pulse therapy (750 mg methylprednisolone intravenously once daily (qd) for three days) and cyclosporine, and was planned for allogeneic bone marrow transplantation. In the course of their hospital stay, the patient's condition deteriorated and after 7 days in the intensive care unit he could not be revived following cardiopulmonary arrest secondary to sepsis and multiple organ failure.

DISCUSSION

HLH is a rare but aggressive and life-threatening syndrome of overactive histiocytes and lymphocytes that commonly affects infants, but is also observed in children and adults of all ages.

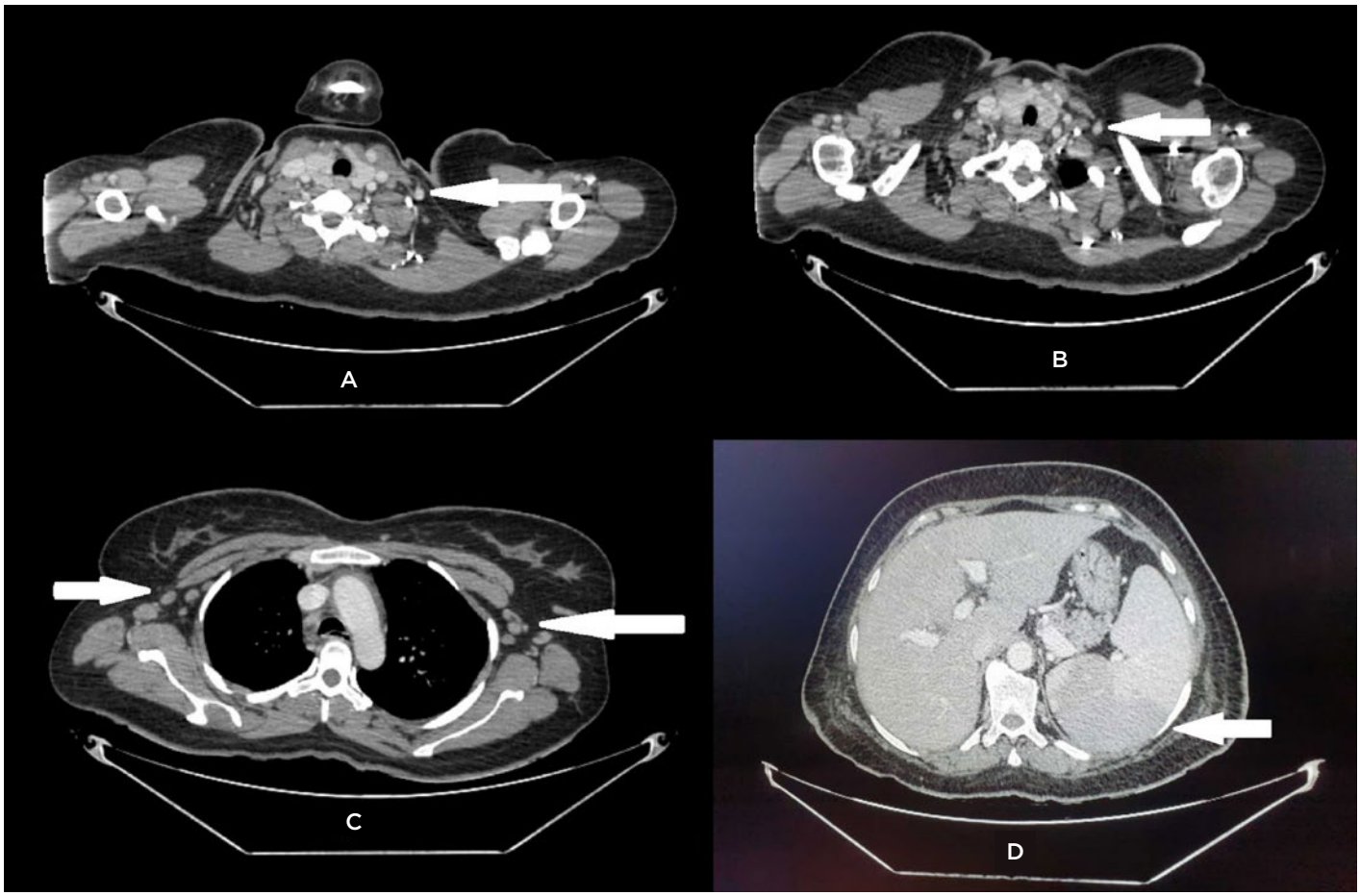

Figure 1: CT of A,B) neck; C) chest; and D) abdomen, showing bilateral cervical and axillary lymphadenopathy and splenomegaly.

The images were provided by Dow University Hospital's medical record with the permission of the relevant head of department. Written consent was obtained from the patient's guardian to include the images for the purpose of medical publication.

Primary HLH, also known as familial haemophagocytic lymphohistiocytosis (FHL), is an autosomal recessive disease caused by a gene mutation of the FHL loci.[4] The incidence of FHL is 0.12 out of 100,000 births annually, with a male-to-female ratio of 1:1,[5] whereas in adults there is a slight male predominance.[6] Secondary HLH, also known as sporadic or acquired HLH, describes patients without a known familial mutation and who typically have a clear trigger for acute HLH development, such as viral infection, autoimmune disease, immunodeficiency, or underlying malignancy. Macrophage activation syndrome is a form of HLH that occurs primarily in patients with rheumatologic diseases, commonly systemic-onset juvenile idiopathic arthritis, adult-onset Still's disease, and systemic lupus erythematosus.[7]

The pathophysiology and aetiology of HLH involve excessive inflammation and tissue destruction due to abnormal immune activation which is caused by the absence of normal downregulation of activated macrophages, NK cells, and cytotoxic lymphocytes.[8] In patients with genetic predisposition, and in sporadic cases with no underlying genetic cause identified, immune activation from an infection is a common trigger. The most common infectious trigger is a viral infection, especially EBV.[9] The worldwide incidence of HLH is reported to be 1.2 cases per million persons per year. This amounts to 1 case per 50,000 births. The age of onset is usually younger than 1 year for the familial form and after 6 years for the secondary sporadic form, but adult-onset has also been reported.[10-12]

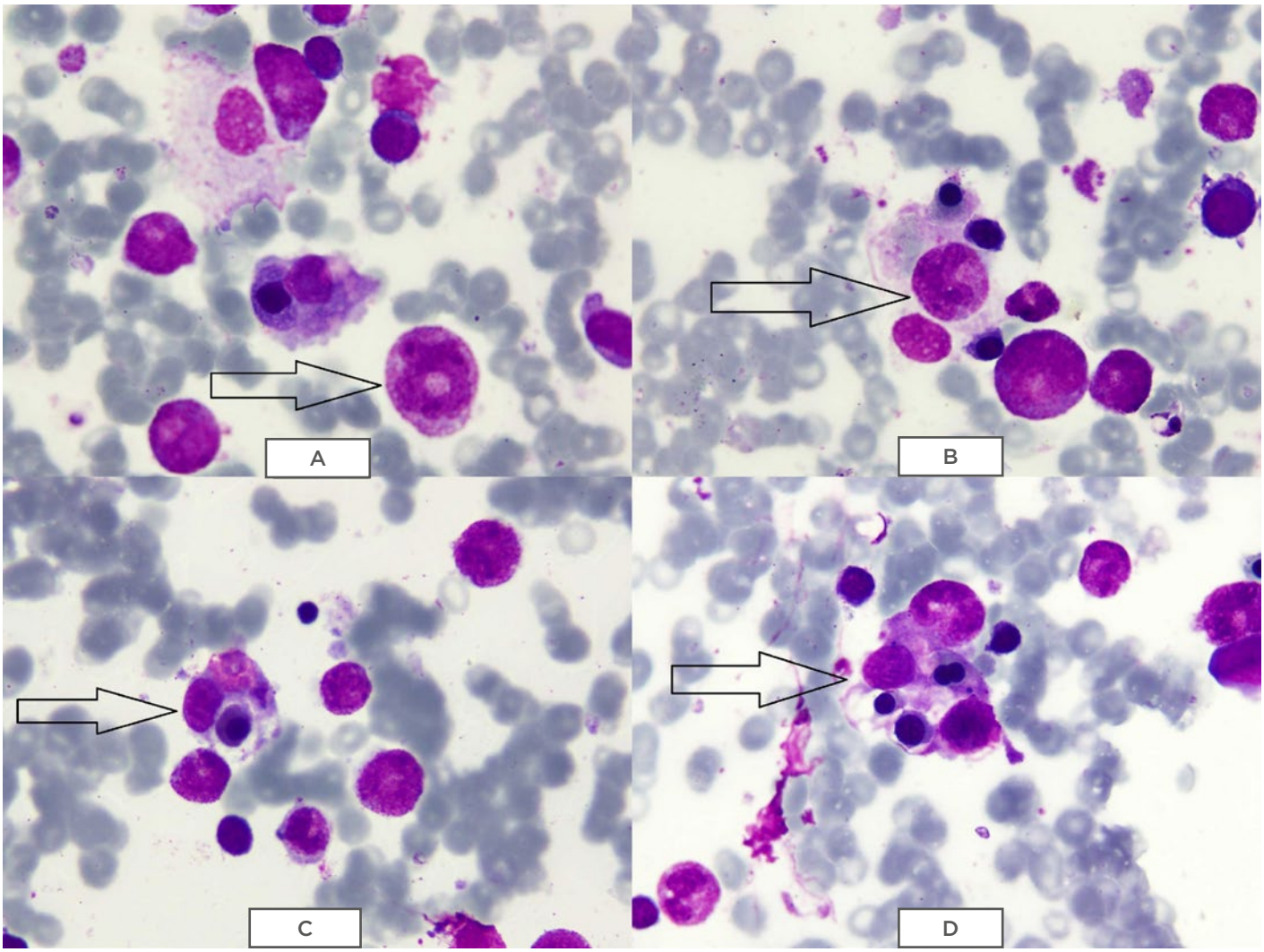

Figure 2: May–Grünwald–Giemsa (MGG) staining of bone marrow showing A,B) phagocytic cells containing erythrocytes and platelets; and C,D) macrophages phagocytising erythrocytes and platelets.

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The presentation of HLH is of a febrile illness associated with multiple organ involvement, presenting as malaise, hepatosplenomegaly, jaundice, generalised lymphadenopathy, and cytopenias.[3] Central nervous system symptoms include seizures, meningitis, encephalopathy, ataxia, hemiplegia, cranial nerve palsies, mental status changes, or irritability seen in up to 75% of paediatric cases.[12] The diagnostic criteria of HLH, introduced by the Histiocyte Society (HS) in 1991,[13] include fever, splenomegaly, cytopenia affecting at least two out of three lineages, hypertriglyceridaemia and/or hypofibrinogenaemia, and haemophagocytosis in the bone marrow, spleen, or lymph nodes. These criteria were updated in 2004[3] to include low or absent NK cell activity measured by the chromium-51 release assay, elevated soluble interleukin-2 receptor a (IL-2Rα/sCD25), and elevated ferritin. Of these eight criteria, at least five are required for diagnosis, although in patients with FHL mutations the diagnosis can be made without meeting five criteria.[14]

The histopathologic findings of HLH include the accumulation of lymphocytes and mature macrophages, which occasionally exhibit haemophagocytic activity, typically seen in the bone marrow but can also occur in the spleen,

lymph nodes, liver, skin, lungs, meninges, CSF, and, rarely, subcutaneous tissue.[15] A definitive diagnosis of HLH can be made by a molecular analysis that includes a demonstration of *PRF1* mutation based on flow cytometry by staining perforin contained in lymphocytes.[16] Mutation analysis should be performed in all HLH cases because the demonstration of a characteristic genetic defect alone can be used to diagnose HLH without five of the eight diagnostic criteria being met.[3,11-14]

A large number of underlying conditions have been reported in association with HLH.[17] The management of HLH aims to suppress the exaggerated immune response using immunosuppressive agents. The second international meeting of the HS in 2004 formulated a treatment protocol for HLH which recommends an 8-week induction therapy with corticosteroids, etoposide, and cyclosporine.[18] Corticosteroids suppress the elevated cytokines, cyclosporine inhibits T-cell activation, and etoposide blocks cell division and proliferation.

Table 1: General characteristics and HLH-probability scores of the patient.

Characteristics	Patient Findings	Score
Age	26	
Sex	Male	
Cause	Adult-onset Still's disease	
Known underlying immunosuppression	No	0
Temperature	>102.9 °F (>39.4 °C)	+49
Organomegaly	Both spleen and liver	+38
Number of cytopenias	2 lineages	+24
Ferritin (ng/mL)	40,000 (>6,000)	+50
Triglyceride (mg/dL)	234.0 (132.7–354.0)	+44
Fibrinogen (g/L)	0.57 (<2.50)	+30
Aspartate aminotransferase (U/L)	247 (>30)	+19
Haemophagocytosis on bone marrow aspirate	Yes	+35
HLH-probability score	289 (>99%)	
Diagnostic criteria met	6/8	

Stem cell transplant is indicated in selective familial cases as it can improve 3-year survival from nearly 0% to 50%. Some cases have reported stem cell transplantation to be curative.[19] The prognosis of genetic HLH without therapy is poor, with a median survival of 1–2 months,[20] and 3-year survival <10%.[18] Macrophage activation syndrome in systemic-onset juvenile idiopathic arthritis has a reported mortality of 8–22%.[7] The overall reported mortality for acquired HLH exceeds 50%. Among all the viruses associated with HLH, EBV carries the worst prognosis, with reported mortality ranging from 25% to 100%.[9] However, the addition of etoposide improves prognosis if given within the first 4 weeks.[7]

In this review of the literature, data mining was performed using the PubMed search engine and Google Scholar, using medical terms involving or similar to 'adult-onset Still's disease associated with HLH.' A variety of cases were found to report an association of HLH with Still's disease. One of the cases presented with severe pancytopenia and jaundice, which are the most likely presenting features of both illnesses.[21] Still's disease usually has a good prognosis with steroids, but the therapy has been reported to cause gastrointestinal ulceration.[22] Rarely, the course of both diseases can be complicated with disseminated intravascular coagulation.[23] *M. pneumoniae* has been known to cause HLH on a background of Still's disease.[24] One review article suggested serum ferritin levels as a diagnostic marker of HLH, and a marker of disease activity for Still's disease. However, hyperferritinaemia can be a feature of many uncommon pathologies including autoimmune, infectious, inflammatory, or neoplastic, where it plays a pro-inflammatory role which can sometimes lead to a cytokine storm.[25] One study suggested the presence of interstitial lung disease is a significant risk factor for developing HLH, as well as relapsing of Still's disease.[26] Lastly, high-dose steroids have been the mainstay of treatment whenever there is an overlapping presence of Still's disease with features of HLH.[27]

CONCLUSION

This case report highlights a case of HLH in association with adult-onset Still's disease, which fulfilled five out of eight defined criteria outlined by the HS, including fever, hepatosplenomegaly, cytopenia, hypertriglyceridaemia, hypofibrinogenaemia, haemophagocytosis in the bone marrow, and elevated ferritin. Treatment focussed on the elimination of the triggering infection, and utilised high-dose glucocorticosteroids along with second-line therapies of cyclosporin, intravenous immunoglobulins, and etoposide, but the patient did not survive.

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