THE 13th WFH GLOBAL FORUM

Advances in Treatments and Technologies for Bleeding Disorders

NOVEMBER 17-18, 2023, MONTREAL CANADA

SUMMARY

WFH
WORLD FEDERATION OF HEMOPHILIA

Summary of the 13th WFH Global Forum on Advances in Treatments and Technologies for Bleeding Disorders

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INTRODUCTION

The 13th WFH Global Forum in November 2023 gathered a diverse group of 128 stakeholders from 32 countries—clinicians, patients, caregivers, patient advocates, clinical investigators, regulatory experts, and industry members— for in-depth discussion of the rapidly evolving field of treatment for congenital bleeding disorders. Remarkable treatment innovations in the last decade such as longer-acting factor concentrates, factor mimetics, rebalancing agents, and gene therapy offer potentially transformative benefits to people with hemophilia. New treatments have also been introduced for von Willebrand disease, other factor deficiencies, and platelet function disorders. However, there are limitations related to cost, availability, and access to treatment, and health inequities in low-income countries and underdiagnosed or underserved populations such as women and girls with bleeding disorders, people with mild/moderate bleeding disorders, and people with very rare bleeding disorders. The Global Forum explored the expanding treatment landscape, clinical practices, challenges, and potential solutions to improve treatment and outcomes for all, particularly for 70-75% of people with bleeding disorders worldwide estimated to be still undiagnosed or have inadequate treatment.

CONFRONTING LIMITATIONS OF THERAPIES

Classification of severity of hemophilia: Do we need a change?

Johnny Mahlangu (University of the Witwatersrand, Johannesburg, South Africa) noted that over the last seven decades, there has been remarkable change in the availability and use of hemostatic agents for treatment of hemophilia.[1] The changing treatment paradigms and range of outcomes that span all severities in hemophilia compel changing the severity classification of hemophilia, he stated.

Prophylaxis is the standard of care for hemophilia worldwide.[1] Current hemophilia classification is based on biological factor level (severe <1%, moderate 1-5%, mild >5%–40%).[2] This approach may leave some patients with suboptimal bleeding control as endogenous factor levels do not always correspond to bleeding phenotype; arthropathy and target joints occur across all severities.[3,4] The armamentarium of treatment today provides many options to personalize treatment: standard half-life (SHL) CFCs, extended half-life (EHL) CFCs, non-factor therapies, and gene therapy, with diverse regimens (high-dose, intermediate-dose, low-dose, dose escalation).[5-16] Treatment for all hemophilia severities should aim to prevent bleeds and help patients achieve optimal outcomes. Prophylaxis should be individualized based on bleeding phenotype, outcomes, joint status, pharmacokinetic profile, and other patient characteristics.[5] New classifications by clinical phenotype are therefore recommended.

Mike Makris (University of Sheffield, United Kingdom) made the case against redefining classifications of hemophilia despite known limitations related to bleeding phenotype and laboratory testing because this approach has served the community well in prognostication and guidance of treatment. In the past, disease monitoring focused on

joint bleeds and other common types of bleeding. At present, monitoring focuses on annualized bleed rate (ABR) and annualized joint bleed rate (AJBR), and the aim of treatment is prophylaxis to prevent bleeds.

In 2023, there has been significant discourse on redefining hemophilia classifications, with monitoring of bleeding symptoms and treatment aiming for good bleed control and health-related quality of life (HRQoL).[17-20] Problems with the proposed re-classification include lack of international standards and common definitions and instruments for assessing spontaneous and traumatic bleeds, ABRs, and joint disease. Disease outcomes should not define disease classification; infants would have to experience bleeding to demonstrate disease severity and a child with <1% baseline factor levels started on new therapy resulting in no joint bleeds and normal quality of life would still have severe hemophilia. Current classifications should continue to be used but may potentially be updated with other measures.

Plasma supply and demand

Over the past 25 years, the use of plasma-derived medicinal products (PDMPs) has greatly increased due to expanding patient needs. From 1996 to 2021, the global market for plasma products grew by 7.5% annually, driven by rising demand for immunoglobulin (Ig) products which now make up 60% of PDMPs.[21] Current global plasma collection and supply fall far short of global patient needs, said Brian O'Mahony (Irish Haemophilia Society).

In 2021, 63% of the global plasma supply originated from North America, mostly from the United States. Europe accounted for 15% of the global supply and Asia Pacific for 21%. North America and Asia Pacific collect sufficient plasma for their regions, whereas other regions have significant deficits in plasma supply and import PDMPs. Most of the global plasma supply is collected by plasmapheresis from voluntary nonremunerated donors, paid donors, or both, depending on national blood systems. In 2022, about 71 million litres of plasma were collected globally; much greater volumes of plasma would be needed to meet the demand for PDMPs, including coagulation factor products.

Most European plasma comes from four countries with both nonremunerated and paid plasma donation: Germany, Austria, Czech Republic, and Hungary. Countries with nonremunerated plasma collection such as Italy, Spain, France, and in the UK have domestic plasma deficits. Addressing the need for significant increases in plasma supply to meet global demand will only be achievable with collection from both types of plasma donors, with government investment of funds to achieve the target.

Orphan inherited bleeding disorders

Magdalena Lewandowska (Indiana Hemophilia and Thrombosis Center, USA) spoke about challenges in treatment of rare inherited bleeding disorders, and outreach and

research needs towards improving clinical care. In most countries, a rare disorder is defined as one that affects in 1,500–2,500 people. In the U.S. it is based on prevalence, affecting less than 1 in 200,000 people in the population.

Challenges in clinical practice include diagnosis, lack of medical training and expertise in rare disorders, classifications of severity, variation in bleeding phenotype, correlation of target assay level and clinical response, and management of adverse effects such as inhibitor formation and thrombosis. From the pharmaceutical perspective, clinical development is complicated by the small numbers affected, high research and clinical trial costs, and regulatory burdens.

Outreach initiatives are needed to raise awareness and training of physicians, hemophilia treatment centre (HTC) medical professionals, and specialists outside the HTC network. There is need for innovative research, recruitment, and training initiatives. The American Thrombosis and Hemostasis Network (ATHN) provides free genetic testing with the objective to enhance genotype and phenotype data on the rare bleeding disorder population and support future research. Focus areas for optimal care include diagnostics, clinical and research infrastructure, regulatory processes for novel therapies, and data collection.[22] A national pathway is needed, with streamlined processes for research funding, evaluation of safety and benefits, post-approval monitoring, centralized data collection, and HTC referrals.[22]

Confronting limitations in treatment of mild and moderate hemophilia

Samantha Gouw (Amsterdam UMC, Netherlands) spoke about the limitations in treatment of mild and moderate hemophilia. While people with mild/moderate hemophilia generally have few bleeds and complications, there is wide variation in bleeding phenotype and some have severe bleeding including spontaneous joint bleeds.[23] A 2011 study of 145 patients with moderate hemophilia A/B found that 81% had at least one joint bleed by the median age of 5; and 25% had bleeding phenotype comparable with severe hemophilia.[24] A 2013 systematic review found in the range of 15-70% of patients with moderate hemophilia had arthropathy.[25] A recent international multicentre study in 2022 showed that patients with mild/moderate hemophilia had musculoskeletal changes in the elbows, knees, and ankles despite having low joint bleeding rates; hemosiderin was found in 14% of bleed-free joints.[26,27]

Data from the WFH 2022 Annual Global Survey show a large gap in diagnosis of mild/moderate hemophilia between high-income countries (40%) and upper middle income (19%) and low/lower middle income countries (12%).[28] Lack of treatment have negative health consequences. A study of mild/moderate hemophilia A based on 1980-2020 data from 35 HTCs in 11 countries found 42% of deaths were related to hemophilia, with 59% associated with intracranial bleeding.[29] Variations in mild/moderate hemophilia phenotype raise questions about which patients are at greater risk for joint bleeds, joint damage, intracranial hemorrhage, and reduced HRQoL. Studies have found patients with above 15-17% FVIII activity had no joint bleeds and no spontaneous joint bleeds above

19-25%.[26,30,31] Clinical guidelines, research, treatment innovations, and individualized treatment strategies based on bleeding phenotype are needed to address the health inequities and ensure optimal care.☐

Optimal therapies: Women and girls with bleeding disorders

Dawn Rotellini (National Bleeding Disorders Foundation, USA) spoke about healthcare inequities experienced by women and girls with inherited bleeding disorders, such as under-diagnosis, inadequate care, and lack of advanced therapies resulting from exclusion from clinical trials.[35] In the United States, 76% of males with VWD are diagnosed by age 10, whereas 50% of females remain undiagnosed by age 12 with an average delay of 16 years between onset of symptoms and diagnosis. In general, there is lack of awareness about mild/moderate bleeding disorders.[35]

In additional to the typical bleeding symptoms in males, bleeding disorders have unique impacts on women and girls at different life stages, such as menorrhagia, iron deficiency, and pregnancy issues which may affect psychosocial, sexual, and reproductive health.[36] Common symptoms such as heavy menstrual bleeding and painful periods may lead to early exposure to hormonal therapy during adolescence. Pre-conception genetic counselling and education is important including on increased bleeding risk during pregnancy and regional anesthesia during childbirth, postpartum bleeding and anemia, pregnancy loss in severe cases, and perimenopausal bleeding issues. One survey found that 78% of women diagnosed with a bleeding disorder had heavy menstrual bleeding, 37% had postpartum hemorrhage, and 76% had bleeding after miscarriage; many had more than four bleeding symptoms.

Women and girls with bleeding disorders require individualized treatment and coordinated hematology and obstetric care. Research is needed on the effects of hormones, menstruation, pregnancy, and perimenopause; the interaction between von Willebrand factor (VWF) and various proteins in regulation of hemostasis and vascular integrity; and the impact of factor levels on bleeding phenotype with aging. Education, access to treatment options, involvement in research clinical and trials, treatment guidelines, and shared decision-making are essential to remove current barriers and improve care.

Platelet transfusions and substitutes

Catherine Hayward (McMaster University, Hamilton, Canada) described platelet transfusion and substitute treatments for inherited platelet function disorders (IPFD), highlighting the need for more research and evidence for optimal diagnosis and management. Platelet transfusion is used to prevent or stop bleeding in patients with low platelet counts or poor platelet function; it is life-saving treatment for some severe IPFDs.[37,38] Limitations include scarce supply, short shelf-life, transfusion reactions, alloimmunization, infection transmission, immunomodulatory risks, poor evidence on

dosing, challenges in assessing platelet response, and perioperative and postpartum thrombosis risks.[39]

Substitutes for platelet transfusion consist of desmopressin (DDAVP), recombinant activated factor VII (rFVIIa), tranexamic acid (TXA), thrombopoietin receptor agonists (TPO-OA). Findings support using platelet-sparing therapies but the best approach remains uncertain due to limited direct evidence and lack of prospective safety and efficacy studies comparing different approaches to non-severe IPFD.[39]

DDAVP, a synthetic vasopressin that promotes platelet adhesion, is the most frequently used therapy for non-severe IPFD.[40] DDAVP prophylaxis has been shown to control bleeding in 59% of patients. [39,41,42] TXA is often used for IPFD despite lack of high-quality evidence.[43,] Limited duration TXA treatment for minor bleeding during surgery and for menorrhagia has shown no increased thrombotic risk. Prolonged TXA treatment for major traumatic bleeding is associated with risk of thrombosis and concurrent thromboprophylaxis carries high thrombotic risk.[43,] Important questions include when to use single therapy with DDAVP or TXA; whether combined DDAVP/TXA therapy increases thrombotic risks in IPFD; and whether multi-day TXA is safe for post-operative or post-partum situations.

rFVIIa has shown overall efficacy as a platelet transfusion substitute for patients with severe IPFD; rFVIIa prophylaxis has shown improvement in patients with recurrent severe bleeding and refractory anemia.[45] TPO-RA briefly increases platelet production to ameliorate bleeding and is used before surgery, chemotherapy, hematopoietic stem cell transplantation.[46] It is important to screen patients for iron deficiency and anemia, which can complicate treatment.[47,]

Limitations of therapies: Hemophilia A (CFCs, GT, factor VIII mimetics)

Margareth Ozelo (Hemocentro Unicamp, Sao Paulo, Brazil) discussed the benefits and limitations of currently available therapies for hemophilia A: standard half-life plasma-derived and recombinant CFCs, extended half-life CFCs, factor VIII mimetics, and adeno-associated virus (AAV) vector gene therapy.

Factor replacement therapy can be individualized for episodic treatment and prophylaxis. The goal of prophylaxis has long been to target at least 3% FVIII activity levels to prevent spontaneous bleeding and joint damage and preserve musculoskeletal function.[1] Recent studies suggest at least 50% FVIII should be targeted, in the mild hemophilia range, to totally prevent joint bleeds.[49,50] The standard half-life of FVIII is 8–12 hours, making 50% FVIII levels difficult to achieve. EHL FVIII such as rurioctocog alfa pegol (PEGylated rFVIII) can achieve 10% FVIII levels and efanesoctocog alfa (rFVIIIFc-VWF-XTEN) can achieve 40% FVIII levels.[49-51] Disadvantages are the need for frequent venous infusion, limited half-life, variation in factor activity (peaks and troughs), and immunogenicity (up to 35% of patients develop FVIII inhibitors).

Factor substitution therapy include factor VIII mimetics such as emicizumab offer several advantages: subcutaneous infusion, steady-state hemostatic levels equivalent to 9-15% FVIII activity, flexible dosing regimens, and better adherence. Emicizumab prophylaxis is very effective; however, it does not provide total bleed protection and concomitant treatment with FVIII or bypassing agents is needed for bleeding episodes and surgical procedures. Preclinical trials of Mim8 showed about 15-fold higher potency than an emicizumab analog.[52] However, FVIII mimetics are not easily monitored and carry risk of thrombosis.

Other approaches include AAV vector-based gene therapy. Clinical studies of AAV5 gene therapy for hemophilia A (valoctocogene roxaparvovec) show stable FVIII activity at normal levels with a single infusion. Disadvantages include variable and unpredictable response, decrease in FVIII expression over time, vector immunogenicity requiring immunosuppression, and potential risk of short-and long-term adverse events. Factors that may affect variability in patient response include FVIII synthesis, transduction efficiency, and factors such as liver health, use of medications, comorbidities, and genetic factors.[53-56] Durability is unpredictable; phase 1/2 trials showed mean FVIII activity of 9.8% lasting up to 6 years.[57,58] Additional gene therapies based on AAV6, AAV8, and rAAVhu37 vectors are in preclinical development.

Limitations of therapies: Hemophilia B (CFCs, GT)

Steven Pipe (University of Michigan, Ann Arbor, United States) described the hemophilia B treatment landscape and the limitations of currently available therapies. FIX is a smaller molecule than FVIII and has 20- to 40-fold higher half-life than FVIII. Another distinction is FIX distribution from the intravascular to extravascular space, with 15-20-fold extravascular FIX than in circulation, which has implications on FIX dosing.[59] Inhibitor formation in patients with severe hemophilia B (4-5%) is lower than in severe hemophilia A (30-40%), however, it is complicated by hypersensitivity to FIX (>60%).

Novel hemophilia B therapies offer higher protection and reduce the burden of treatment for patients. A large proportion of patients in high-income countries have switched to EHL prophylaxis.[60] A Canadian study of patients switched from SHL or EHL FIX to nonacog beta pegol (N9-GP) showed significant reductions in ABRs.[61] Patient-reported outcomes of recombinant FIX Fc fusion (rFIXFc) include reduced pain, increased physical activity levels, long-term QoL improvements, and high QoL scores in pediatric patients. Dose and frequency of FIX prophylaxis should be adapted to clinical phenotype and lifestyle factors, and not exclusively on plasma trough levels.[62] There are limitations in the ability for EHL FIX to achieve expected outcomes. Patient-reported outcomes show similar ABRs with SHL and EHL FIX; 76% patients had mild or moderate chronic pain and 70% had ≥ 2 bleeding events per year.[60] Laboratory requirements for product-specific monitoring of EHL FIX should be considered.[62]

The first gene therapy for hemophilia B, etranacogene dezaparvovec, was approved in 2022.[63-65] Clinical trials showed 98% of patients, both with and without AAV5 neutralizing

antibodies (NAbs), expressed FIX activity in the mild to normal range; 75% had sustained FIX activity levels >25% at 24 months post-treatment.[66] Two patients did not express endogenous FIX; one had high AAV5 NAbs (3,212 titers) and another with AAV5 NAbs received only 10% of the planned dose.[66] All responders had 76-87% decrease in ABR for all types of bleeding.[66] Studies based on 5-8 years' data showed durable response, statistically significant efficacy and better bleeding outcomes compared to EHL FIX, nominal improvements in HrQoL, and no significant improvement in physical functioning or pain.[67,68] Further intervention is needed in patients with osteochondral damage and advanced joint disease. Other limitations include substantial variability in steady-state levels and no predictability for individual outcome.[69]

Limitations of therapies: Hemophilia A and B rebalancing agents

Pratima Chowdary (Royal Free Hospital, London, UK) gave an overview of approved and investigational non-factor/non-replacement therapies for treatment of hemophilia A and B. These novel therapies are effective particularly for patients with inhibitors. Mainstay treatment for inhibitors consists of immune tolerance with high- or low-dose FVIII/FIX regimens and procoagulant bypassing agents rFVIIa and activated prothrombin complex concentrate (aPCC). Limitations include the need for frequent infusions, variability in individual patient response, and high cost of treatment.

FVIII mimetics which circumvent FVIII deficiency by augmenting thrombin generation offer more effective prophylaxis with steady-state factor levels and reduced treatment burden. Some challenges remain related to cost, breakthrough bleeding, need for CFCs or bypass agents for bleeding episodes, and laboratory monitoring.

Rebalancing agents are inhibitors of natural coagulants used to restore hemostasis, such as inhibitors of tissue factor inhibitor pathway (concizumab, marstacimab), antithrombin (fitusiran), and activated protein C (Serpin PC). Benefits include reduction in treatment burden, bleeding risk, annualized bleeding rates, and treatment costs; applicability to multiple bleeding disorders; and potential for use in combination therapies.[70] Rebalancing agents are particularly useful for addressing the unmet needs of hemophilia B patients with inhibitors and those with less than optimal response to other therapies.

Challenges of non-factor replacement therapies include individual variability in thrombin generation, thrombotic risks, asymptomatic bleeding, change in baseline phenotype, and lack of clear monitoring strategies.[71] There is need for new surveillance strategies for joint outcomes; biomarkers for assessment of dose response and outcomes; categorization of responders; and defined boundaries for treatment efficacy and safety.[72,73] Clinician and patient education on the evolution of clinical bleeding symptoms, thrombotic risks, use of concomitant therapies, and disease management are needed.

Real world implications of antibodies and assay issues in gene therapy

Radoslaw Kaczmarek (School of Medicine, Indiana University, USA) discussed issues related to assays for neutralizing AAV antibodies against wild-type AAV prior to gene therapy and anti-AAV vector antibodies post-dosing. Anti-AAV antibodies may diminish transgene expression and are used to assess gene therapy eligibility and potential impacts on efficacy.[74] The cell-based transduction inhibition assay (TI) uses rAAV vector encoding a reporter gene to measure the ability of plasma or serum samples containing NAbs and non-antibody neutralizing factors to reduce cell transduction.[74] The total antibody assay (TAb) is an immunoassay (eg, ELISA or ECLA) that measures anti-AAV antibodies regardless of neutralizing activity.[74] High seroprevalence of antibodies to all AAV viruses, with geographic variations, may lead to antibodies to AAV vectors used in gene therapy.[75,76]

Establishing clinically relevant screening titer cut-offs is complex.[74] An international study of anti-AAV immune responses in healthy cohorts found 87% of those with NAbs against multiple serotypes had higher anti-AAV2 titers than anti-AAV5 and anti-AAV8, suggesting cross-reactivity of anti-AAV antibodyserotypes.[76] Currently, hemophilia patients who test positive for anti-AAV antibodies are mostly excluded from gene therapy. However, a Phase 2b study of AAV5 gene therapy for hemophilia B, etranacogene dezaparvovec, showed efficacy in patients with anti-AAV5 NAbs up to 340 titers.[77] Clinical trials of AAV5 gene therapy for hemophilia A, valoctocogene roxaparvovec, showed good correlation between AAV5 TI and TAb test results. The product was approved with a TAb companion diagnostic test for eligibility screening. A Phase 3 trial in patients with anti-AAV5 NAbs showed lower to no FVIII expression compared to patients without anti-AAV5 NAbs.

Key limitations of these assays are lack of standardization and the use of different parameters, which make it unfeasible to make titer comparisons when both types of assay are used. TAb and TI assay results may be confounded by cross-reactive anti-AAV antibodies. In addition, there is more variability between TI assays due to u different cell lines used, serum volumes, and gene vector multiplicity (vector particles per cell). There is need for better understanding of differences between AAV serotypes, antibody responses, and cross-reactivity, and the implications for gene transfer, and strategies to mitigate the effects of anti-AAV antibodies in patients.

INEQUITIES IN HEALTH CARE DELIVERY

Affordability of global bleeding disorders treatment

Brian O'Mahony (Irish Haemophilia Society) spoke about the implications of EHL CFCs, factor mimetics, and gene therapy on hemophilia treatment costs, affordability, and procurement globally. Despite expanding treatment options and competitive pricing, hemophilia remains an expensive condition to treat and access to effective treatment continues to be a challenge in many countries. Procurement of treatment products is complex, given differences in efficacy and variation between list prices and actual prices from country to country. Key challenges are high list prices and limited available

information on procurement prices making price negotiations difficult and payer inflexibility about high-cost treatments relative to benefits such as improved efficacy and reduced treatment burden.

In high-income countries, the complex mix of therapies available is leading to a shift away from simple tenders to multi-criteria decision analysis. Framework agreements allow the procurement process to move forward with specific conditions to be agreed later and dynamic purchasing systems open tenders to any company that meets the selection criteria. For novel therapies, price can be compared to treatment cost per patient per year. For gene therapy, which has unknown long-term durability and safety effects, outcome-based or annual payment models may be based on cost of prophylaxis per year for an agreed number of years. Hemophilia treaters and national patient organizations need to be knowledgeable about pricing trends and involved in procurement processes.

Emicizumab: Low-dose or non-standard interval doses

Alfonso Iorio (McMaster University, Hamilton, Canada) described low-dose and non-standard dose prophylaxis with emicizumab.[78,79] Low-dose emicizumab strategies enable feasible access in resource-limited countries, reduce costs, and eliminate drug wastage. There is strong safety and efficacy evidence based on clinical studies in 858 patients in 10 countries across North America, Central America, Europe, Africa, and Asia. Preliminary dose-finding studies suggested plasma emicizumab levels around 50 µg/mL should result in zero bleeding events for one year in at least 50% of patients; and levels around 100 µg/mL should result in zero bleeding events in all patients.[80]

Bodyweight-adjusted dosing of emicizumab often results in doses that do not match the vial content. The rationale for entire vial low-dosing (rounded to nearest vial size) is based on multiple factors: linear pharmacokinetics; unachievable dose precision; bodyweight fluctuation; less potential for dosing errors; and reduced treatment burden. [79,81] A retrospective study found savings of 600 mg/dose without significant sub- or supratherapeutic dosing, with cumulative annual savings of $1,793,549.76.[81] Other studies showed good bleeding control and decreases costs without negative impacts on outcomes.[79,82]

Real-world experience of low-dose emicizumab in Malaysia showed greatly reduced ABRs and no thromboembolic events.[83] A study in India on low-dose emicizumab every 1-4 weeks, reported emicizumab plasma concentrations of 3.3−20.7 µg/mL at 1 week and no treated bleeding events.[84] In Finland and Japan, low-dose emicizumab (0.3 mg/kg/week) showed significantly improved ABRs; and higher doses (1 mg/kg, 3 mg/kg) led to zero bleeds.[85,86] Many studies have examined thrombosis and thromboembolic risk with emicizumab.[87-92] Data from the FDA Adverse Event Reporting System show three times as many thrombotic events with emicizumab compared to FVIII. Emicizumab data show wide heterogeneity in phenotype and response, confirming the importance of personalized treatment.[93-95]

Bispecific antibodies in low-income countries: lessons from the Humanitarian Aid Program

Cedric Hermans (Cliniques universitaires Saint-Luc, Brussels, Belgium) described efforts by WFH to facilitate access to emicizumab in LMICs through the Humanitarian Aid Program. Critical steps include product shipping and importation; cold-chain storage and distribution; identification of candidates; documentation of usage; and. monitoring of outcomes and adverse events. Enrollment criteria in order of priority are patients age 0-12 with inhibitors; age >12 with inhibitors; age 0-12 without inhibitors but with history of life-threatening bleeds, ABR >8, or poor venous access; and >age 12 without inhibitors who have a history of life-threatening bleeds, ABR >8, or poor venous access.

In 2023, 1,155 patients in 34 countries received emicizumab through the humanitarian aid program. In Sub-Saharan Africa, WFH provided emicizumab to 433 patients (July 2019–July 2022). Bleed rates decreased and several minor and major surgeries were performed without bleeding complications; 11 adverse events were reported, with no cases of thrombosis, thrombotic microangiopathy, anti-drug antibodies, treatment stoppage, or death related to emicizumab. Most patients had no bleeds and reduction in pain, emergency hospital visits, school/work absenteeism, and family stress.

Using BT200 (rondaptivon pegol) in countries with limited access to CFCs

The cost of factor replacement therapy can present significant barrier to optimal management of hemophilia. James C. Gilbert (Band Therapeutics, USA) presented BT200 (rondaptivon pegol), a pegylated VWF-binding aptamer shown to prolong FVIII and VWF half-life as a potential avenue for improving access to CFCs in resource-limited settings. Early clinical trials in healthy volunteers (single dose of 0.18-48 mg) and patients with severe hemophilia A (3–9 mg dose weekly in combination with different FVIII regimens) showed BT200 blocks VWF/FVIII clearance and elevates VWF and FVIII.[96-98]

BT200/FVIII combination therapy could potentially offer greater convenience and protection for patients with severe hemophilia A or VWD in high-income countries, and greater impact for patients in low-income countries with limited FVIII allocation. Phase 2/3 clinical trials will also study single BT200 therapy in patients with non-severe hemophilia A and patients with type 1 or type 2 VWD. Andrea Edginton (University of Waterloo, Canada) noted that dose-dependent BT200 and FVIII therapy can achieve prolonged FVIII levels above 3%; 30 IU/kg FVIII dosing and 12 mg of BT200 once weekly resulted in 10% FVIII levels. Thus, BT200 may enable greater bleed protection with limited amounts of FVIII. Low-dose FVIII prophylaxis augmented with BT200 is being explored in collaboration with WAPPS-Hemo.

INEQUITIES IN HEALTHCARE DELIVERY AND INNOVATIVE ACCESS PROGRAMS

Achievements and challenges in gene therapy trials in low-income countries

Ulrike Reiss (St. Jude Children's Research Hospital, Memphis USA) presented an update on the global clinical trial of gene therapy for moderate/severe hemophilia B. Patients have achieved 5-7% FIX levels persisting more than 10 years to date, with significant reduction in bleeding frequency, factor use, and complications, and increased quality of life.[99-105] A phase 2 clinical trial in the United States and in low-income countries (Sri Lanka, Nepal, Thailand, Vietnam, Peru) is evaluating patient and clinician needs related to gene therapy education and decision-making. Studies will also evaluate payment models and g cost-effectiveness, with micro-costing analysis of gene therapy versus local standard of care.

A key objective is to describe infrastructure, operational, and regulatory needs for site implementation, such as local regulatory support, and drug and lab sample shipments by specialist courier. Important considerations include country and institution policies and regulations on gene therapy; clinical research; privacy of personal data; cross-border transfer of data and materials; storage of supplies; surveillance and mitigation measures; timeframe variability; contracts and approvals; language barriers/translation needs; patient education and compliance; and staff training needs.

Achievements and challenges in establishing a gene therapy trial in India

Alok Srivastava, (Christian Medical College, Vellore, India) described the journey towards India's first-ever clinical trial of gene therapy in 2021, on autologous hematopoietic stem cell transplantation (HSCT) in patients with severe hemophilia A. The first application to initiate a gene therapy clinical trial was filed in 2004; however, immune response to transduced hepatocytes, with elevation of liver enzyme levels and reduced FIX level led to stoppage of the trial prior to completion of regulatory review in India.[106].

Over the past 10 years, CMC Vellore has worked with Emory University and the University of Florida to bring together transgene and vector technologies to design a transgene similar to that of University College London (UCL) and St. Jude's Hospital, with promoter modifications and codon optimization. Comparisons showed similar dose-dependent expression and led to a phase 1 clinical trial of lentiviral vector gene therapy for hemophilia A. Human hematopoietic CD34+ stem cells derived from cord blood hemophilic and NSG mouse models and showed significant FVIII expression. Clinical trial submission was filed in 2018 but regulatory review was delayed almost three years by the COVID-19 pandemic; India's first-ever gene therapy clinical trial was approved in 2021.

The phase 1 clinical trial aims to assess the safety and feasibility of autologous hematopoietic stem cell transplantation (HSCT) in patients with severe hemophilia A, and collect efficacy data by monitoring ABRs and CFC consumption. The clinical trial process involves patient conditioning for HSCT; hematopoietic stem cell mobilization using granulocyte-colony stimulating factor (G-CSF) and Plerixafor; apheresis of CD34+ stem cells; *ex vivo* transduction using CD68-ET3 lentiviral vector targeting 80% FVIII activity

levels; transplantation of modified autologous mobilized CD34+ cells (>2x106 CD34+/kg); post-transplant FVIII replacement until engraftment and clinical recovery; monitoring of engraftment, adverse events, and FVIII levels; and safety and efficacy follow-up. Follow-up at 9 and 15 months showed one patient had 3.5% FVIII activity post-treatment which rose to steady 8% FVIII activity; another had 1.5% FVIII activity which increased to steady 3-4% FVIII levels. Both patients had dramatic reduction in bleeds per year. The transduction protocol was modified to enhance FVIII expression and two patients subsequently showed higher FVIII in the mid-range of normal.

Sanofi: Global Health Access Programs

Sanofi's Rare Disease Humanitarian Program delivers therapies to patients with demonstrated need where access to treatment is limited. In 2014, Sanofi and Sobi became visionary sponsors of the WFH Humanitarian Aid Program, together pledging to donate up to 1 billion IU of factor for hemophilia treatment over 10 years, the single largest donation of CFCs in history. As of 2023, they have donated over 700 million IUs of CFCs used to treat over 20,000 people in over 50 countries, said Cecile Le Camus (Global Medical Affairs Hemophilia, Sanofi). The program provides access to medicines according to defined medical criteria and guidelines. Considerations include patient age, disease severity, immigration status, commercial timing, reimbursement/insurance policy issues, budget limitations, product registration, and rare disease legislation. Since 2015, factor donations have been provided treatment for acute bleeds and surgeries in over 22,000 patients and prophylaxis for 2,800 patients.

Pfizer: Equity in hemophilia and the Accord Program

Pfizer's Accord Program provides access to its medicines on a not-for-profit basis to lower-income countries, including hemophilia treatment products such as recombinant CFCs, aminocaproic acid, and tranexamic acid, said Lisa Wilcox (Global Medical Lead, Hemophilia). Through this program, Pfizer works with governments to evaluate treatment needs and develop institutional frameworks and effective solutions that address health system barriers. The program currently provides hemophilia medications, education, and training support to Ghana, Malawi, Senegal, and Rwanda.

Pfizer's Global Hemophilia Grant for Equity in Therapeutic Patient Education provides support to patient advocacy groups and other non-profit organizations for hemophilia education and training initiatives that address local needs, barriers, gaps, and opportunities for action related to treatment. Six grants have been awarded to date. Since 2001, Pfizer has been the exclusive supporter of the WFH Twinning Programs, which partner HTCs and patient organizations with counterparts in different countries to share information, best practices, resources, and strategies to improve management of care for people with bleeding disorders.

Roche: Innovative access strategies for emicizumab

Martynas Aizenas spoke about Roche's comprehensive approach to supporting access to emicizumab. As of 2023, emicizumab has been approved in 120 countries for treatment of hemophilia A with inhibitors; in 108 countries for hemophilia A without inhibitors; and in 64 countries for both indications. It is estimated that more than 22,000 patients receive emicizumab prophylaxis worldwide; 42% of the countries are in the high-income category. Barriers to access to in low- and middle-income countries include lack of healthcare infrastructure and medical professionals, low awareness and diagnosis of hemophilia, lack of patient support, regulatory challenges, general economic pressures, and inadequate health funding and insurance.

Roche's global access strategy consists of inclusive clinical trials, acceleration of regulatory filings and reimbursement approvals, partnerships for infrastructure development, and increasing awareness among health authorities about the value of investment in hemophilia treatment. It partners with key stakeholders to enable access to emicizumab through innovative approaches such as supplementary insurance schemes, subscription models, and pay-for-performance agreements. Differential pricing for emicizumab considers specific factors: unmet needs, clinical benefits, and impacts on patient quality of life, impacts on overall healthcare costs, availability of other treatment options, and a country's relative income and ability to pay.

In 2019, Roche signed a partnership agreement with the government of Côte d'Ivoire to expand access to Roche medicines for cancer, hepatitis B, chronic renal anemia, and hemophilia A.[107] WFH twinning and prophylaxis initiatives led to recognition of the importance of hemophilia treatment. Access to emicizumab was made possible in April 2021. Clinical outcomes of emicizumab prophylaxis in Ivory Coast compared to the UK showed similar outcomes can be achieved and the potential to profoundly modify the burden and impacts of hemophilia in low-income countries.[88,108]

KEYNOTE

Learning from the past and preparing for the future

André Picard, health and science journalist at The Globe and Mail in Canada and author of The Gift of Death: Confronting Canada's Tainted-Blood Tragedy (1998) presented on the crisis caused by blood products contaminated with HIV and HCV in the 1970s and 1980ss. CFCs and derivatives are produced by pooling plasma from numerous donation sources. Despite pathogen testing protocols, the emergence of HIV led to a widespread surge of infections. Over 4,600 infections were reported in the U.K., 1,750 in Australia, and 2,000 in France. Overall, about half of all people with hemophilia in the western world developed HIV/AIDS.

In Canada, about 2,000 people contracted HIV/AIDS and 30,000 people were infected with HCV. The Canadian Red Cross was slow to implement HIV screening in blood

collection, underestimating infection risk and fearing interruption in donation rates. This resulted in prolonged use of highly contaminated blood products in hemophilia treatment; this was later repeated with Health Canada's failure to adequately screen donors for HCV. Recommendations from the Krever Commission Inquiry in 1997 led to an overhaul of the blood system, the creation of Canadian Blood Services, and compensation for the victims totaling about $5 billion. No cases of HIV infection through blood products have been reported since. The tainted blood tragedy remains the costliest failure in Canadian public health history.

Today, advancements such as emicizumab offer new, more effective treatment but side effects may yet emerge with long-term use. Rigorous post-marketing safety surveillance continues to be essential, especially in the case of gene therapies with limited longitudinal data and significant potential for harm.

WFH PROGRAMS

Global impact of WFH Humanitarian Aid Program

In 2015, the WFH Humanitarian Aid Program set forth to secure more predictable and substantial clotting factor donations with long shelf lives. By 2023, 1.65 billion IU of CFCs had been donated and distributed to 87 countries—more than six times the amount over the preceding 19 years said Assad Haffar, WFH Humanitarian Aid Director. During this time, over 5,000 people with hemophilia received prophylactic treatment, over 75% of whom were children under 11 years of age. There were 3,850 patients treated with CFCs and 1,150 patients received prophylaxis with non-replacement therapies. More than 4,600 surgeries were performed, including 446 life and limb-saving surgeries and over 1,000 major surgeries.

Challenges in establishing effective prophylaxis programs in low-resource settings include decision-making on treatment criteria and patient prioritization, adherence, compliance, home treatment, inhibitor monitoring, intravenous access, management of breakthrough bleeds, and outcome measures. The program provides training on logistics, distribution, transportation, handling, storage, usage, registry data collection, and reporting of adverse events. Assessment of selected countries has ensured good compliance.

The WFH's key goals moving forward are to secure donations of bypassing agents, VWD products, and novel therapies, and explore gene therapy donations. Sincere gratitude is extended to founding visionary contributors Sanofi and Sobi; visionary contributors Bayer, CSL Behring, Chugai, Genentech, and Roche; and leadership contributors Grifols, Takeda, and the Japan Blood Products Organization (JBPO) for making this possible.

WFH Registries: World Bleeding Disorders Registry and Gene Therapy Registry

Mayss Naccache, Head of the WFH Gene Therapy Program, gave an overview of WFH's three key data collection tools: the WFH Annual Global Survey (AGS), World Bleeding Disorders Registry (WBDR), and Gene Therapy Registry (GTR). Since 1999, the AGS has collected country-level data from national member organizations on number of patients identified with hemophilia and other inherited bleeding disorders and usage of treatment products. The yearly data and estimations are useful for evaluation, benchmarking of care in different countries, and advocacy for access to safe and effective treatment.

The WBDR started to collect clinical data from HTCs on treatment and outcomes in 2018. It has been integral to improving clinical care and advocacy and comparing outcomes in different countries. From 2018 to 2023, WBDR enrolled 13,120 people with hemophilia from 119 HTCs in 45 countries, and 676 people with VWD from 30 HTCs in 20 countries. WBDR also tracks patients receiving humanitarian aid treatment, which increased from 74 patients in 2020 to 1,973 patients in 2023.

The GTR collects demographic and clinical outcomes data from national and local registries for the assessment of long- treatment safety and efficacy of gene therapies. It monitors adverse events such as inhibitors, thromboembolic events, autoimmune disorders, malignancies, liver disease, and hypersensitivity reactions. A Scientific Advisory Board provides direction on scientific activities and policy decisions. A steering committee oversees registry design and implementation and a subcommittee representing participating HTCs oversees data usage, exchange, and standardization. The governance structure ensures independent and transparent evaluation of safety events and reporting of data.

In 2023, the European Medicines Agency endorsed GTR for its consolidation of international data on patients with hemophilia undergoing gene therapy and its value for post-approval safety and efficacy studies. It also recommended the GTR for phase 4 studies of new gene therapies, which will be critical to advancing gene therapy for hemophilia on a global scale.

WFH Shared Decision-Making Tool

Donna Coffin, WFH Director of Research and Education, presented the WFH Shared Decision-Making (SDM) Tool for hemophilia gene therapy launched in August 2023. This web-based platform aids patients and clinicians in making informed decisions about gene therapy, balancing the risks and expected outcomes with clinical evidence. The tool educates users on five treatment classes (SHL CFCs, EHL factor CFCs, factor mimetics, rebalancing agents, and gene therapy), through videos and factsheets based on product monographs and information from regulatory agencies. A comparative table allows users to evaluate key attributes of each treatment class, such as eligibility, administration, efficacy, and potential safety risks (eg, hypersensitivity reactions, inhibitor formation, thrombotic events).

The SDM tool is updated regularly with new data and disseminated via an online program and in-person trainings for NMOs, patients, and HTCs. For patients in countries without access to gene therapy, the SDM tool can be used for education and advocacy. WFH extends gratitude to sponsors for funding and support for the SDM tool: BioMarin, CSL Behring, Pfizer, Novo Nordisk, and Spark Therapeutics.

WFH Advocacy: Essential Medicines List

The WHO Essential Medicines List (EML) presents medicines for priority conditions needed for every healthcare system and for priority diseases such as hemophilia, selected based on efficacy, accessibility, safety, and cost-effectiveness.[109] It consists of "core" and "complementary" lists which are used as guidance by many countries, forming the basis of 137 national essential medicines lists, with variations aligned to country priorities. WHO revises the EML every two years based on applications for additions, deletions, or changes and evidence of a medicine's safety, efficacy, and cost-effectiveness. Glenn Pierce, WFH Vice President, Medical, spoke about issues with WHO's EML update in 2023, the negative impacts on access to effective treatments, and potential safety risks for people with hemophilia.

Cryoprecipitate is effective for hemophilia A, VWD, fibrinogen deficiency, FXIII deficiency. It is safe if produced using Quality Plasma Program criteria for viral screening, which have been in place in high-income countries as a result of contamination of the blood supply in the 1970s and 1980s. Many low-income countries do not have state-of-the art virus detection methods such as nucleic acid testing; viruses such as HIV and HCV can pass into the blood supply and infect patients, especially in endemic countries. Pathogen-reduced cryoprecipitate (PR cryo) is produced using different technologies to inactivate lipid-enveloped viruses (eg, HIV, HCV, HBV, Zika) in small pools—it does not inactivate non-lipid enveloped viruses (eg, HAV, parvovirus B19). PR cryo is approved for inherited bleeding disorders in a few lower-income countries. Little data is available on cost-effectiveness in comparison to CFCs.

In Fall 2022, WFH was approached to support an application by the International Coalition for Safe Plasma Proteins (ICSPP) to add PR cryo to the WHO EML. The WFH hemophilia treatment guidelines (2020) specify that cryoprecipitate is only to be used in limb- and life-threatening bleeding situations when no CFCs are available, and that non-viral-inactivated cryoprecipitate is a high risk for bloodborne infections in countries that do not have adequate assays and quality control to ensure the safety of thei blood supply. WFH wrote a letter of non-support for inclusion of PR cryo for bleeding disorders in the WHO EML, asserting the risks and noting that the cost of plasma-derived and recombinant CFCs can be as low as or less than PR cryo.[110] The letter also stated that cryoprecipitate cannot be used for prophylaxis, the global standard of care for hemophilia, nor for home therapy due to the need for storage at sub-zero temperatures.[110]

WHO's 2023 EML added PR cryo as a core medicine and listed cryoprecipitate as an alternative modality. FVIII and FIX CFCs are listed as complementary medicines. WFH communicated with WHO to reiterate the treatment recommendations for hemophilia and morbidity and mortality risks in countries that strongly adhere to the EML in setting national medicines lists but changes will not be made until the 2025 EML update. WFH has requested that hemophilia be removed from the indications for PR cryo and for cryoprecipitate to be removed from the EML.

GENE THERAPY MARKET ACCESS AND ECONOMICS

Insights from first health technology assessments of gene therapies for hemophilia A and B

David Rind (Institute for Clinical and Economic Review, USA) presented on ICER's role in assessing treatment value which influences FDA price negotiations. U.S. drug prices are set by manufacturers in lieu of a government body. In 2022, ICER evaluated two gene therapies, etranacogene dezaparvovec for hemophilia A and valoctocogene roxaparvovec for hemophilia B.

Clinical trials of etranadez showed greatly curtailed bleeding rates, with 80% reduction in treated joint bleeds and 77% reduction in treated bleeds. Mean levels of FIX activity varied. Adverse effects included liver enzyme elevations, headaches, flu-like symptoms, and infusion reactions. ICER gave etranadez a B+ rating, noting small-to-substantial health benefits. Clinical trials of valrox resulted in 84% reduction in treated bleeds and joint bleeds. FVIII activity declined from 42 IU/dL at 12 months to 24 IU/dL at 24 months. Adverse events included liver enzyme elevations, headaches, nausea, arthralgia, and fatigue. ICER gave valrox a C++ rating, noting concerns about long-term durability and potential harms.

A 2022 ICER policy paper estimated the full cost offsets of etranadez and valrox, calculating fair price for etranadez to be $9.9 million and $6.7 million for valrox, based on traditional value-based pricing models. Since prices are primarily driven by cost offsets from existing therapies, ICER proposed capping cost offsets at $150,000/year or assigning only half to gene therapy. This adjustment would lower the fair price to $2.93–2.96 million for etranadez and $1.96 million for valrox.

Promoting global access to innovation: The challenge for gene therapy in hemophilia

Louis Garrison (CHOICE Institute, USA) discussed health economic issues related to newly available gene therapies for hemophilia, notably, the high upfront costs in relation to the potential for substantial health gains and healthcare cost offsets over many years. The "economic value" of a medicine refers to the health and life year gains, improvements in clinical response and quality of life, reduction of morbidities, cost savings and offsets, and what patients are willing to pay. A key challenge with gene therapies is the limited

longterm data available and uncertain longterm benefits, durability, and product lifecycle.[111]

Different HTA methods are used. The US incorporates quality-adjusted life years (QALY). ICER's review of valrox gene therapy for hemophilia A identified a durability issue compared to hemophilia B gene therapy. FDA delayed approval pending two more years of data. ICER made a number of recommendations. Durability assumptions should be based on clinical evidence, expert input, and biological plausibility. Real-world clinical and QoL data should be collected in registries to help address uncertainties. Logistical barriers need to be addressed to facilitate assessment of clinical evidence and comparative effectiveness based on single-arm trials. Valuation of cost offsets should use real-world comparator costs and cost comparisons should take a lifetime perspective. Finally, strategies such as pooled procurement enable better price negotiations, broader access, and large health gains for a greater number of patients. Outcome-based contracts can be explored to address cost uncertainties due to uncertainties about the long-term outcomes.

Access pathways to gene therapy

Germany

Johannes Oldenburg (Institute for Experimental Haematology and Transfusion Medicine) spoke about challenges and regulatory issues related to introducing gene therapies. Germany licensed the first gene therapy for hemophilia A in August 2022; the cost was set as €2.25 million. The first gene therapy for hemophilia B was licensed in February 2023 and expected to cost about €3.5 million. BioMarin proposed a pay-for-performance model for valoctocogene roxaparvovec, based on an initial payment and a prophylaxis-free interval of 12 years, with proportional payback if 8 years are not reached and the patient returns to prophylactic treatment. The cost of the comparator therapy EHL FVIII is €275,000 per year, and €400,000 per year for prophylaxis with the FVIII mimetic emicizumab. CSL Behring proposed annual payments for etranacogene dezaparvovec, corresponding to the average yearly cost of prophylaxis for a hemophilia B patient for 10-15 years. The cost of EHL FIX therapy is about €265,000 per year.

HTA assessment in Germany is conducted by the regulatory authority (G-BA), followed by a 15-month period for bilateral price negotiations between the company and health insurance payers. Costing is based on evidence-based medical benefit assessments using data from clinical trials and any additional value. For both gene therapies, additional value was not quantifiable. Germany has adopted a hub and spoke model for delivery of gene therapy. Patients may be referred by HTCs for gene therapy at a specialized gene therapy dosing center. Close communication and clear division of responsibilities regarding patient education, eligibility testing, informed consent, reimbursement, gene therapy infusion, and follow-up between centers are necessary. Documentation of gene therapy and compliance with the Quality Assurance Guideline for the Use of Advances Therapy Medicinal Products is required.

China

Renchi Yang (Institute of Hematology and Blood Diseases Hospital, Tianjin, China) gave an overview of gene therapy initiatives in China. From 2021 to 2023, China's National Medical Products Administration (NMPA) approved seven hemophilia clinical trial applications from six China-based manufacturers: Belief Biomed, Vitalgen, Real and Best Biotech, Grit Science, and Frontera Therapeutics. There are 21 hemophilia A patients and 19 hemophilia B patients enrolled in investigator-initiated trials (IIT), and 3 hemophilia A patients and 19 hemophilia B patients in investigational new drug (IND) trials.

Three types of primary health insurance and subsidies are provided for hemophilia patients in China. Basic medical insurance is provided to people who are employed, unemployed, or out of the labour force; the ceiling for reimbursement is $450,000 CNY. Critical illness insurance is also available and government subsidies and complimentary medicines from pharmaceutical companies are provided to severely vulnerable groups. In addition, the Hainan Boao Lecheng International Medical Tourism Pilot Zone permits use of FDA-licensed or CE-marked pharmaceuticals through medical institutions that engage with multinational pharmaceutical companies. The first patient in China to receive gene therapy for hemophilia B was dosed in the United States on June 22, 2023, paid by the patient. The first gene therapy product for hemophilia may be approved by NMPA in 2025 in China.

South Africa

Most clinical trials of investigational gene therapies globally are being done in North America, Europe, and East Asia; very few in low-middle and low-income countries. In Africa, only South Africa is engaged in gene therapy research and development, at a single site in Johannesburg. [112] Johnny Mahlangu (University of the Witwatersrand, National Health Laboratory Service), spoke about the evolving pathway for gene therapy research and development in South Africa.

The high cost of gene therapy limits access to gene therapy globally and increase global disparities in health and access to effective treatment.[113] In 2022, the World Economic Forum identified strategies to accelerate access to gene therapy in LMICs. A sustainable gene therapy pathway encompasses all aspects from research and development, medical facilities, capacity building, manufacturing, and workforce, to funding, policy development, and market access. LMICs can proactively build capacity by integrating gene therapy within national and institutional plans.[114] The biggest challenges are lack of diagnosis and access to treatment and competing public health needs, such as HIV and cancer which affect millions of people without access to effective treatment.

South Africa has adopted a multi-disease approach to research, development, and manufacturing of gene therapies for HIV, hemophilia, and sickle cell disease which leverages programs already in place. Advanced medical infrastructure and genomic

analysis facilities put in place during the COVID-19 pandemic are being repurposed for gene therapy. A streamlined process is being developed, encompassing gene therapy conception, vector generation, regulatory activities, manufacturing, clinical training, and delivery of gene therapy. Several access models are being explored, including global clinical trial participation, strategic partnerships with manufacturers, and national health insurance coverage. Alternative reimbursement models are being pursued (amortization, reinsurance, risk sharing/outcome-based payment) through streamlined outcome-based regulatory pathways.

HOT TOPICS

Desmopressin acetate (DDAVP)

Nathan Connell, (Harvard Medical School, USA) gave an update on DDAVP, a synthetic drug used for prophylaxis, treatment of bleeding, and minor surgical procedures in mild/moderate hemophilia A and type 1 VWD. It is also used to treat platelet function abnormalities and mild factor XI deficiency. Evidence from case reports suggests DDAVP has some benefit as surgical prophylaxis for patients with FXI deficiency and as treatment for bleeding episodes in patients with type 2N VWD.[115] Despite significant variations in individual response, DDAVP is an important treatment option that helps avoid the need for blood/plasma-derived products.[116]

VWD guidelines recommend DDAVP as treatment primarily for patients with type 1 VWD and baseline VWF levels of <0.30 IU/mL, after testing to determine to DDAVP response. Studies have used varying definitions for DDAVP response. A proposed definition for future research and clinical practice is "an increase of at least 2 times the baseline VWF activity level and a sustained increase of both VWF and FVIII activity levels >0.50 IU/mL for at least 4 hours."[117]

A 2022 study found that DDAVP response depends on the presence and type of genetic variants in patients with type 1 and type 2 VWD.[118] Another study showed DDAVP response in female VWD patients may vary across the lifespan; no age-related change in response was observed in male patients.[119] Studies have shown good response to subcutaneous DDAVP, with a slightly longer time for absorption and action.[120,☐]

In 2020 Ferring Pharmaceutics initiated a precautionary voluntary global recall of all batches of its desmopressin nasal spray products. The root cause of the out-of-specification results was identified as a vial sealing issue. Ferring is installing new machinery and a new assembly line. In some countries, compounding pharmacies (eg, STAQ Pharma, USA) have produced intranasal DDAVP products to temporarily filled the gap. Elsewhere, patients are using alternative options: intravenous and subcutaneous DDAVP, antifibrinolytics, aminocaproic acid, and factor products. The global shortage is expected to persist until early 2025.

Pipeline for new VWD therapies

Sophie Susen (Lille University Hospital, Lille, France) spoke about VWD treatment and investigational drugs in clinical development. For over 30 years, the mainstay of VWD treatment consisted of intermediate-purity concentrates containing FVIII and VWF and high-purity plasma-derived and recombinant FVIII concentrates to treat or prevent bleeding; DDAVP (type 1, type 2A, type 2M VWD); and adjuvant therapies such as antifibrinolytic agents and tranexamic acid used for mucosal bleeding and in surgical settings. Plasma-derived VWF was introduced in 2005 and recombinant VWF introduced in 2015.[122] There is wide variability in VWD clinical practice and level of evidence.

New treatment options include prophylaxis with emicizumab, a FVIII mimetic used in hemophilia A and recently approved for VWD in the U.S. and Japan. It is injected subcutaneously and has a half-life of about 4 weeks, which allows biweekly or monthly injections, substantially reducing treatment burden.[122] Clinical studies in type 3 VWD patients with and without anti-VWF antibodies showed marked improvement in hemostasis; successful prevention of hemarthrosis and major spontaneous bleeds; substantial improvement in menorrhagia and quality of life; and reduction in joint bleeds, hospitalization, transfusions, and hospital costs.[122-124] Recent *in vitro* studies showed improvement in thrombus formation under shear in all VWD types, suggesting potential for use in type 1 and type 2 VWD.[124]

Several investigational nonfactor therapies are in clinical development. Pegylated VWF-binding aptamer BT200 (rondoraptivon pegol) decreases VWF and FVIII clearance to prolong VWF half-life. A prospective phase 2 clinical trial in type 2 VWD showed more than twofold increase in VWF/FVIII levels, and threefold increase in platelet counts.[125] BT200 may also have potential for other VWD types. KB-V13A12, a nanobody-based bifunctional albumin-VWF binding molecule, has been tested in a type 1 VWD mouse model; subcutaneous administration was shown to increase plasma VWF levels by twofold for up to 10 days.[124] Other novel nonfactor therapies for VWD include approved and investigational rebalancing agents such as antithrombin-targeted RNA interference molecule (fitusiran), anti-TFPI inhibitors (concizumab, marstacimab), activated protein C (APC) and protein S antibodies, aPC serine protease inhibitor (SerpinPC), bispecific FVII-binding antibody (HMB-001), and next-generation FVIII mimetics (NXT700, Mim8). Gene therapy for VWD is in very early preclinical stages.

These novel emerging therapies have potential for use in multiple types of VWD and may help address health and treatment inequities related to VWD and the unmet needs of specific populations such as patients with anti-VWF antibodies and patients with menorrhagia and other uterine bleeding problems.

NXT007: FIXa and FX bispecific antibody

Keiji Nogami (Nara Medical University, Kashihara, Japan) presented on NXT007, an investigational FIXa and FX bispecific antibody developed through optimization of the

heavy chains of emicizumab combined with two new non-common light chains. NXT007 increases co-factor activity of FVIIIa and thrombin generation, resulting in a more potent agent with improved pharmacokinetic profile and long half-life. It shows potential to achieve non-hemophilia hemostatic ranges in people with hemophilia A.

A preclinical study in a hemophilia A monkey model showed NXT700 increase hemostatic activity within the non-hemophilic range.[126] A phase 1/2 clinical trial in healthy volunteers showed single subcutaneous doses of NXT007 were well tolerated with no thromboembolic events and mean elimination half-life of 10 weeks. Preliminary data presented at ISTH 2023 from an ongoing phase 1/2 clinical trial in adults with moderate/severe hemophilia A has shown good hemostatic control in patients without antidrug antibodies; some patients developed anti-NXT007 antibodies. Pharmacodynamics was assessed; APTT was shortened and thrombin generation was promoted in a dose-dependent manner. There were no dose-dependent increases in incidence of adverse events and no thrombotic events nor injection-site reactions. Immunogenicity of multiple doses and higher dose levels in hemophilia A cohorts is under currently evaluation.

Mim8: activated FVIIIa mimetic

Steve Lentz (University of Iowa Carver College of Medicine, USA) presented a novel FVIIIa mimetic called Mim8, an IgG4 bispecific antibody that binds to activated FIX and FX, enhancing FIXa activity by over 20,000-fold and thrombin generation. It is administered as a single fixed dose once monthly, weekly or every two weeks. Phase 1/2 clinical trials showed dose-dependent increase in plasma concentrations of Mim8 with mean elimination half-life of 30 days, similar to emicizumab. Few patients experienced bleeds and there were no unexpected safety concerns, dose-dependent adverse events, and thromboembolic events. There was no occurrence of anti-Mim8 antibodies and no dose-dependent changes in coagulation parameters (D-dimer, FIX, FX, fibrinogen, platelets).[127]

The phase 2 trial in 42 adolescent and adult patients with hemophilia A, including 4 patients with inhibitors, showed stable increased plasma concentrations of Mim8 in each cohort over the 12-week trial.[128] Two randomized cohorts for weekly and monthly dosing achieved almost identical steady-state Mim8 plasma concentrations and comparable steady-state peak thrombin levels which increased with dose. An exploratory biomarker trial in a cohort of patients with and without inhibitors on emicizumab showed that Mim8 triggers and increases thrombin peak at lower concentrations than emicizumab. Phase 3 trials are currently underway using a tiered dosing schedule based on dosing frequency and three body weight ranges, with target exposure level within the range of 2.7 to 18 µg/mL.

Marstacimab: anti-TFPI monoclonal antibody

Davide Matino (McMaster University, Hamilton, Canada) gave an update on marstacimab, a novel human IgG1 monoclonal antibody against TFPI, administered subcutaneously

once weekly to rebalance hemostasis in hemophilia A or B patients with or without inhibitors. The Phase 3 trial of marstacimab in 116 patients with severe hemophilia A and moderately severe/severe hemophilia B without inhibitors (on-demand n=33, prophylaxis n=83) showed over 90% reduction in ABRs compared to prior on-demand factor replacement therapy and 35% reduction in ABRs compared to prior routine prophylaxis. Consistent bleed rates were found in the long-term extension study of 87 patients treated for up to 16 months, with continued improvement shown in the prophylaxis cohort.

Overall, marstacimab was safe and well tolerated in patients dosed for up to 2.3 years. Treatment-related adverse events occurred in 12.1% of the on-demand cohort and in 22.9% of the prophylaxis cohort. No thrombotic events occurred. There were 23 cases of antidrug antibodies which had no impact on marstacimab safety; titers were low and successfully resolved in 22 cases.

Concizumab: anti-TFPI antibody

Pratima Chowdary (Royal Free Hospital, London, UK) presented on concizumab, a subcutaneous anti-TFPI antibody agent for once daily prophylaxis across all hemophilia subtypes. It works by blocking TFPI, allowing independent activation of FXa and sufficient thrombin generation for coagulation. Clinical trials have demonstrated efficacy in hemophilia A and B patients with and without inhibitors, with a proportion of patients with zero ABRs. Thrombotic events in three patients in the phase 3 trials resulted in a trial pause. The events consisted of renal infarct in a hemophilia B patient with inhibitors; acute myocardial infarction in a hemophilia A patient at two months; and deep vein thrombosis, pulmonary embolism, and venous thrombosis in a hemophilia A patient at three months. All three cases were resolved.

A risk mitigation strategy was developed with guidance on potential drug-drug interaction during the management of bleeds with replacement therapy. The study was restarted with a revised dosing regimen using the same loading dose of 1 mg/kg and a lower maintenance dose of 0.20 mg/kg once daily (previously 0.25 mg/kg). Testing of concizumab levels at week 4 led to further adjustments to maintenance dose levels. No thromboembolic events were reported after restarting treatment with the new regimen.[129] Concizumab was approved in Canada for the treatment of hemophilia B and hemophilia A patients with inhibitors in 2023; and in Japan the same year.[130,131] In the US, the FDA has requested more information on measures to ensure correct monitoring, testing, and dosing in clinical practice.

Fitusiran: investigational siRNA therapeutic agent

Alok Srivastava (Christian Medical College, Vellore, India) gave an update on fitusiran, a siRNA agent with GalNAc conjugates designed to inhibit antithrombin expression and restore sufficient thrombin generation to rebalance hemostasis in people with hemophilia A or B, irrespective of inhibitor status.[71,132-134] Phase 3 trials in hemophilia A and B patients with and without inhibitors in 26 countries showed sustained reduction in AT levels, with

90% reduction in bleeding rates compared to on-demand bypass agent/factor and 61% reduction compared to prior bypass agents/factor prophylaxis.[134-136] About 20-25% of patients had ALT/AST elevations which were classified as non-serious and mild-to-moderate in severity.[134-138] A mandatory halt was imposed in 2021 to investigate a fatal cerebral venous sinus thrombosis, which was deemed to be unrelated to fitusiran. A revised dosing regimen based on PK/PD modelling and target AT levels of 15%-35% has been implemented. The regimen adjusts dose and frequency based on individual response. It is expected that 90% of patients will require one or no dose change and 80% of patients will be treated once every 2 months.

CRISPR/Cas9-based gene editing for hemophilia B

Meagan O'Brien (Regeneron Pharmaceuticals, USA) presented an investigational intravenous gene therapy for hemophilia B based on CRISPR/Cas9-mediated F9 *in vivo* gene insertion into the albumin locus, using lipid nanoparticles to mediate durable FIX expression. CRISPR/Cas9 gene editing for hemophilia may offer advantages over AAV-mediated episome-based gene therapies. Insertion of the transgene sequence specifically into targeted site increases durability and possible utility in pediatrics, where unmet need is most acute. Superior expression with F9 gene insertion obviates the need to use hyperactive variant gene sequence (Padua). In addition, the promoterless transgene alleviates concerns related to integration of promoter-containing sequence.

Preclinical data showed restoration of robust and stable FIX expression in nonhuman primate and mice for one year and persisting following liver growth and regeneration. In primates, robust FIX activity was measured in plasma even with FIX insertion in low percentage of albumin loci. Experiments in neonatal mice showed durable and stable FIX expression through adulthood. FIX expression in non-human primates was functionally indistinguishable from purified human FIX. IND and clinical trial submissions were anticipated at end of 2023. A lead-in clinical study has opened in the UK, US, Canada, and Germany, and an interventional study is anticipated mid-2024.

Be Biopharma: Developing Engineered B Cell Medicines for People with Hemophilia B

Krishnan Viswanadhan (Be Biopharma, USA) described current development of a single-dose gene therapy, BE-101, an *ex vivo* precision gene engineered B-cell medicine that produces active and sustained FIX levels for treatment of hemophilia B. Engineering of B lymphocytes which are produced lifelong by the immune system may offer an alternative to recombinant and plasma-derived factor treatment, may provide continuous endogenous FIX production that can persist for decades.[139-141] Factor replacement therapies carry multiple disadvantages: repeated infusions/injections, short half-life, potential breakthrough bleeds, reactions to recombinant proteins, and immune intolerance.[142]

Be Biopharma engineers B cell medicines which produce durable and constant levels, with no pre-conditioning. B-cell medicines are titratable, tunable, redosable, allogeneic

and autologous, and mitigate insertional mutagenesis risk. Preclinical studies have shown stable protein production; a single dose persisted in mice past 1 year and engraftment in nonhuman primates was successful. BE-101 for hemophilia B has demonstrated engraftment, biological activity and long-term *in vivo* secretion of FIX in nonclinical mice studies.[143] Pivotal studies are underway and pre-IND feedback has been received from FDA. BE-101 is advancing towards a first-in-human clinical trial in mid-2024 for people with moderately severe to severe hemophilia B.

Acronyms and Abbreviations

AAV	adeno-associated virus (AAV2, AAV5, AAV5-hFIX-Padua, AAV6, AAV8, AAVhu37)
ABR	annualized bleed rate
ADA	anti-drug antibody
AJBR	annualized joint bleed rate
AGS	Annual Global Survey
ALT	alanine transaminase
aPCC	activated prothrombin complex concentrate
aPTT	activated partial thromboplastin clotting time
ASH	American Hematology Society
AST	aspartate aminotransferase
AT	antithrombin
ATHN	American Thrombosis and Hemostasis Network
CE	Conformité Européenne (mark of compliance for European Economic Area)
CFC	clotting factor concentrate
CSA	chromogenic assay
CT	computed tomography
DDAVP	desmopressin (1-desamino-8D-arginine vasopressin)
ECLA	electrochemiluminescence assay
EHL	extended half-life
Emicizumab	FVIII mimetic bispecific monoclonal antibody
EML	essential medicines list
ELISA	enzyme-linked immunosorbent assay
FDA	U.S. Food and Drug Administration
FIX, FIXa	factor IX (nine), activated FIX
FIX-Padua	FIX Padua variant
FVIII, FVIIIa	factor VIII (eight), activated FVIII
FX, FXa	factor X (ten), activated FX
FXI	factor XI (eleven)
FXIII	factor XIII (thirteen)
GT	gene therapy
HAV, HBV, HCV	hepatitis A, B, C
HEK	human embryonic kidney cells
HEK293	human embryonic kidney cell line 293
HeLa	human epithelial cells
HIV	human immunodeficiency virus
HRQoL	health-related quality of life
HSCT	hematopoietic stem cell transplantation
HTA	health technology assessment
HTC	hemophilia treatment centre
Huh-7	Huh-7 cells
ICER	Institute for Clinical and Economic Review
ICSPP	International Coalition for Safe Plasma Proteins
IHTC	International hemophilia treatment centre

IIT	investigator-initiated trial
IND	investigational new drug
IPFD	inherited platelet function disorder
IVIG	intravenous immunoglobulin
LMIC	low- and middle-income country
MRI	magnetic resonance imaging
NAb	neutralizing antibody
NBDF	National Bleeding Disorders Foundation, USA
NMO	National Member Organization
NMPA	National Medical Products Administration, China
NSG	NOD scid gamma mouse
OSA	one-stage clotting assay
PDMP	plasma-derived medicinal product
PR cryo	pathogen-reduced cryoprecipitate
PTT	partial thromboplastin clotting time
PUPs	previously untreated patients
QALY	quality-adjusted life year
QoL	quality of life
rAAV	recombinant AAV viral vector
rAAVhu37	recombinant AAV serotype hu.37
rFIXFc	recombinant FIX-Fc fusion protein
rFVIIa	activated recombinant factor VII
rFVIIIFc	recombinant FVIII-Fc fusion protein
rFVIII/VWF-Fc	recombinant FVIII/VWF-Fc fusion protein
SCIG	subcutaneous immunoglobulin
SDM	shared decision-making
SHL	standard half-life
TAb	total antibody assay
TI	transduction inhibition assay
TPO-OA	thrombopoietin receptor agonists
TXA	tranexamic acid
ULN	upper limit of normal
VWD	von Willebrand disease (type 1, type 2 and subtypes 2B, 2M, 2N, type 3)
VWF	von Willebrand factor
WAPPS-Hemo	Web-Accessible Population Pharmacokinetics Service for hemophilia
WFH	World Federation of Hemophilia
WHO	World Health Organization

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