

News from the Hemophilia 2010 World Congress in Buenos Aires, Argentina

Challenges and innovations in the treatment of bleeding disorders

The management of patients with bleeding disorders can be challenging for the treating hematologist. It is difficult to outline an appropriate algorithm that covers therapy for all types of bleeding disorders, as this depends on the specific diagnosis, the bleeding problem that requires treatment, the development of inhibitory antibodies, and the presence of comorbidity. Many of the challenges, as well as innovations, in the treatment of bleeding disorders were addressed at a scientific symposium held at the recent Hemophilia World Congress. The symposium was chaired by two highly renowned experts: Prof. Jorge DiPaola of the University of Colorado in Denver, Colorado, USA, and Prof. David Lillicrap of Queen's University in Kingston, Ontario, Canada. This synopsis summarizes the key information from the four presentations of this symposium, which addressed the progress in the therapy of bleeding disorders, immune tolerance induction (ITI) for hemophilia A, the clinical challenges within the aging hemophilia population, and prophylaxis in bleeding disorders.

Progress in therapy of bleeding disorders

Dr. Garrett Bergman, Senior Director of Medical Affairs at CSL Behring, King of Prussia, Pennsylvania, USA, provided a corporate presentation highlighting a selection of the global research/pre-clinical, clinical and post-marketing pipeline of coagulation products. CSL Behring, a world leader in the plasma protein biotherapeutics industry, "Is committed to saving lives and improving the quality of life for people with rare and serious diseases worldwide," explained Dr. Bergman. CSL Behring manufactures and markets a range of safe and effective plasma-derived and recombinant therapeutic proteins. Their therapies are used in the treatment of various conditions, such as immune deficiency diseases, inherited emphysema, and congenital bleeding disorders. Dr. Bergman's presentation reviewed three key coagulation products: one that has received regulatory approval; one that is in clinical development; and one that is in the research/pre-clinical phase.

Helixate® youth Quality-of-Life (HyQoL) studies

CSL Behring has designed two prospective, non-interventional trials to specifically assess the health-related quality of life (HRQoL) of adolescent and young adult hemophilia pa-

tients receiving treatment with the recombinant factor VIII (FVIII) concentrate, Helixate®. As Dr. Bergman explained, the impact of hemophilia and its treatment on patient HRQoL are often overlooked as a primary evaluation criterion in hemophilia clinical trials. Moreover, the impact of transitioning from adolescence to young adulthood and the associated challenges, experiences and expectations of this transition have not been well examined. The trials, which will be conducted in Canada (HyQoL-Canada) and Europe (HyQoL-Europe), aim to evaluate HRQoL and to identify specific determinants impacting HRQoL. Additional information, including clinical parameters, socio-demographics, physical activity, and changes in treatment, living, and working situations, will also be assessed over 36 months. Most previous work assessing HRQoL in hemophilia has been cross-sectional and very few longitudinal studies exist. Information will be obtained using both generic and hemophilia-specific instruments. According to Dr. Bergman, "These studies will help to develop a greater understanding of what life is like for these patients, and what their specific healthcare needs are. They will also help us to identify key transitional life events that might have an impact on HRQoL, and to what extent they do, so that we can anticipate and give guidance and counseling when they are about to undergo such a key life event".

Biostate® SWIFT program

The current global clinical development program SWIFT [Studies with von Willebrand factor (VWF)/FVIII] is just one of many ongoing initiatives that CSL Behring is sponsoring in its continuous efforts to broaden treatment options for hemophilia and von Willebrand disease (VWD). According to Dr. Bergman, CSL Behring has a heritage of innovation in developing bleeding disorder therapies and making a difference in patients' lives. The SWIFT program is evaluating the pharmacokinetics, efficacy, and safety of Biostate®, a low-volume, highly active, plasma-derived VWF/FVIII concentrate that contains a large proportion of high-molecular-weight VWF multimers and an average ratio of VWF to FVIII of approximately 2.2 to 1. The SWIFT program, which includes centers in Europe, North America and South America, consists of four open-label, multi-center studies in children and adult/adolescent patients with hemophilia A or VWD (► Table 1). Patient criteria are outlined in Table 1.

Recombinant factor IX-fusion protein program

An ongoing research focus of CSL Behring is the use of albumin fusion protein technology to extend the half-life of therapeutic proteins. Prophylactic treatment of hemophilia B with the recombinant factor IX (rFIX) protein, for example, requires intravenous administration every 2–3 days to prevent spontaneous bleeding (1). The inconvenience of this approach can affect compliance. The need for a longer acting preparation of rFIX that would allow for less frequent dosing led to the development of the recombinant FIX-albumin fusion protein, rIX-FP (2). The rIX-FP is created by genetically fusing recombinant human albumin to the C-terminus of rFIX via a cleavable linker sequence between rFIX and albumin. "This linker is derived from the same cleavage site responsible for the proteolytic activation of FIX," said Dr. Bergman, "so recombinant FIX-FP will remain in the circulation until it is needed, when it will be activated, cleaving the linker, and separating the FIX and albumin moieties of the fusion protein".

The rIX-FP was evaluated in pre-clinical studies. In the tail-snip bleeding model in the FIX-deficient mouse, rIX-FP corrected the prolonged bleeding time in a dose-dependent

Table 1: Biostate® SWIFT program. HA, hemophilia A; NSB, non-surgical bleeding; PK, pharmacokinetics; PTPs, previously treated patients; VWD, von Willebrand disease.

Study	Hemophilia A SWIFT-HA	Hemophilia A SWIFTLY-HA	VWD SWIFT-VWD	VWD SWIFTLY-VWD
Patients	<ul style="list-style-type: none"> ● Phase II ● ≥50 PTPs with severe hemophilia A (≤1%) ● ≥12 years 	<ul style="list-style-type: none"> ● Phase III ● 20 pediatric PTPs with severe hemophilia A (≤1%) ● <12 years 	<ul style="list-style-type: none"> ● Phase II/III ● 25 patients with VWD (type 1, 2A or 3) ● ≥12 years 	<ul style="list-style-type: none"> ● Phase III ● 12 patients with VWD (type 1, 2A or 3) ● <12 years
Objectives	Primary: <ul style="list-style-type: none"> ● Hemostatic efficacy; PK (≥12 patients) Secondary: <ul style="list-style-type: none"> ● Safety 	Primary: <ul style="list-style-type: none"> ● Hemostatic efficacy; PK Secondary: <ul style="list-style-type: none"> ● Safety 	Primary: <ul style="list-style-type: none"> ● Hemostatic efficacy; PK; efficacy of prophylaxis vs. on-demand therapy Secondary: <ul style="list-style-type: none"> ● Safety; ● Hemostatic efficacy during surgical procedures 	Primary: <ul style="list-style-type: none"> ● Hemostatic efficacy; PK Secondary: <ul style="list-style-type: none"> ● Safety

manner, an effect that was comparable to that of wild-type rFIX and the commercial rFIX product, BeneFIX®. In addition, the pharmacokinetic profile of rIX-FP was assessed in rats and rabbits. The terminal half-life of rIX-FP was up to five-fold longer than either wild-type or plasma-derived rFIX (► Fig. 1). These pre-clinical results demonstrate that fewer infusions of rIX-FP might be required to achieve the same therapeutic effect as that of wild-type FIX. This extraordinary improvement in pharmacokinetics may translate into clinically meaningful benefits: for patients with hemophilia B, the prolonged half-life of the fusion protein may allow for less frequent injections while providing the same safety and efficacy. This is very exciting news for patients, commented Dr. Bergman, and CSL Behring plans to commence a clinical trial of rIX-FP soon as part of their hemophilia B program.

Immune tolerance induction in patients with hemophilia A

Approximately one-third of all patients with severe hemophilia A develop an immune response to therapeutically administered FVIII, resulting in the production of inhibitory antibodies that neutralize the coagulant activity of FVIII (3). Management of these inhibitory antibodies requires sustained and repeated exposure to intravenous FVIII through various ITI protocols. Although first reported in 1977 (4), our current knowledge about ITI derives predominantly from several small heterogeneous

cohort studies and analysis of registry data. Prof. Jan Astermark of the Center for Thrombosis and Hemostasis at the Skåne University Hospital in Malmö, Sweden, reviewed our current knowledge of ITI – its therapy, potential targets, mechanisms of action, and characteristics of success.

Potential ITI targets and mechanisms of action

Some of the targets that could potentially modulate the FVIII-specific immune system by ITI include:

- FVIII-specific memory CD4⁺ T-cells
- FVIII-specific memory B-cells
- Anti-FVIII antibody-producing plasma cells.

“The data we have clearly indicate that the two targets that we probably modulate in one way or another are the memory T-cells as well as the B-cells,” explained Prof. Astermark.

Several immunological mechanisms for inducing tolerance have been suggested, including clonal deletion, clonal anergy (failure to respond to FVIII), clonal ignorance (‘blinded’), receptor editing (changes of antibody structure with no antigen binding), induction of T-regulatory cells, and anti-idiotypic antibodies, but the exact mechanism(s) remain unclear.

ITI regimens

Eradication of the inhibitor by ITI is generally accepted as the best treatment option for patients with inhibitors, as it allows the resump-

tion of FVIII replacement therapy and prophylaxis (5). Various ITI regimens have been utilized, with success rates of approximately 60–80% in good-risk patients. In those who fail initial attempts at ITI, additional treatments, using agents, such as rituximab, may be beneficial, although data supporting therapy with rituximab are preliminary, and the long-term effects remain unknown.

ITI outcome

Several registries have been established to document the outcome of clinical studies of ITI, including the International Immune Tolerance Registry (IITR) (6), the North American Immune Tolerance Registry (NAITR) (7), and the German Registry (8). Findings from these registries show success rates of around 50–80%. Although patients in these registries were treated with different ITI regimens and the definitions of success varied, two characteristics were consistently linked to success in all registries:

- Inhibitor titer before the start of ITI: <10 Bethesda units (BU)/ml
- Peak historical titer: <200 BU/ml.

“However, we do not have any clear cut-off values, but these values are what we consider to be good predictors of success,” said Prof. Astermark.

Other potential factors influencing the outcome of ITI include the duration of inhibitor before the start of ITI, the coexistence of infections or other processes activating the immune system, interruption of ITI, genetic parameters, and the type and purity of concentrate used. In

addition, the use of high-dose protocols appears to reduce the time required to achieve tolerance.

Role of VWF for ITI success

One of the ongoing issues concerning optimal ITI protocols is whether VWF-containing plasma-derived products are more effective at inducing tolerance than high-purity FVIII concentrates. This issue was first raised in a retrospective review of the Frankfurt experience (9). This group had reported a traditionally high ITI success rate with plasma-derived, VWF-containing FVIII concentrates. However, when patients were switched to a high-purity FVIII product, the ITI success rate was considerably lower (90% vs. 29%). In addition, in patients in whom immune tolerance could not be induced with a high-purity FVIII concentrate, switching to a VWF-containing FVIII product resulted in successful ITI in 80% of them. These findings have since been supported by other studies in Germany and Italy, but more data are needed to fully appreciate these observations. Moreover, findings from in vitro studies indicate a lower risk for immunogenicity with VWF-containing products (10, 11).

The rationale for the potential role of VWF-containing FVIII products in successful ITI remains unclear, but several benefits have been suggested, including: (i) steric hindrance (VWF blocks the binding of inhibitory antibodies to the FVIII light chain); (ii) protection of FVIII degradation (prolonged exposure to the immune system); and (iii) immune-modulatory effects.

ITI summary and recommendations

Prof. Astermark concluded his presentation with a summary of ITI recommendations, which are outlined in ► Table 2.

Clinical challenges within the aging hemophilia population

An increasing number of patients with hemophilia are living longer and more productive lives, owing to improved factor replacement therapy, prophylaxis, and comprehensive care programs. This fact, coupled with the general aging of the population, means that a larger proportion of hemophilia patients are experiencing

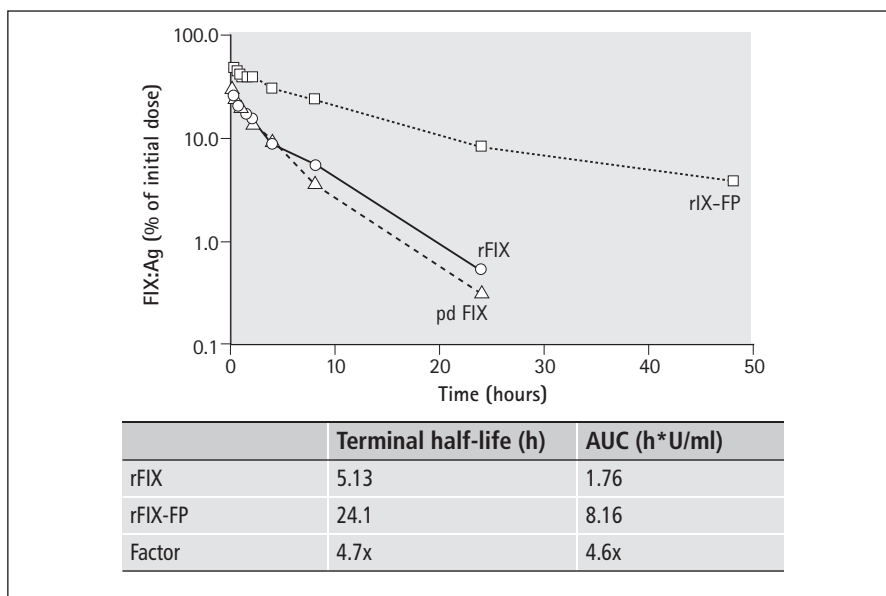


Figure 1: Pharmacokinetics of factor IX (FIX) in rats. Ag, antigen; AUC, area under the curve; pd, plasma derived; rFIX, recombinant FIX; rIX-FP, rFIX albumin fusion protein. Adapted from Metzner HJ, Weimer T, Kronthaler U, et al. Genetic fusion to albumin improves the pharmacokinetic properties of factor IX. *Thromb Haemost* 2009; 102: 634–642 with permission from Schattauer Publishers ©2009.

Table 2: ITI summary and recommendations. BU, Bethesda units; FVIII, factor VIII, ITI, immune tolerance induction; VWF, von Willebrand factor.

ITI recommendation	<ul style="list-style-type: none"> • Low-responding inhibitors in children if inhibitor persists >6 months • Low-responding inhibitors in adults if inhibitor persists and bleeds cannot successfully be treated with replacement therapy • All high-responding inhibitors (>5 BU) – use same type of concentrate as that which was used at the time of detection
Predictors of ITI success	<ul style="list-style-type: none"> • Low pre-ITI titer • Low peak inhibitor titer • Patient genetics
ITI therapy	<ul style="list-style-type: none"> • Use high doses to more rapidly induce a negative Bethesda titer and reduce risk of bleeds • Consider switching ITI protocols when a significant (e.g. 50%) reduction in inhibitor levels cannot be achieved within the first 6–12 months • Consider discontinuation of ITI when no further significant decline in inhibitor levels occurs for 6 months • Consider VWF-containing FVIII products in patients who fail the initial attempt of ITI with high-purity FVIII concentrates • Consider immune-suppression in patients with high-level, long-standing inhibitors not responding to other treatment (optimal immune-suppressive agent still unclear) • Consider new ITI attempts

comorbidities – not only those typically associated with hemophilia, such as chronic pain and arthropathy, but also those related to aging, such as cardiovascular disease (CVD) and arthritis. But how do we optimize healthcare delivery to these aging hemophilia patients? Prof.

Barbara Konkle from the Puget Sound Blood Center, University of Washington, Seattle, Washington, USA, presented an update on the current understanding of the aging male hemophilia population and the clinical challenges they face.

The aging hemophilia patient

"The hemophilia population is not unique – more and more patients are reaching old age and are facing many chronic medical conditions," said Prof. Konkle (12, 13) (► Fig. 2). "Only recently are data becoming available to help guide us in managing the comorbidities of this population". Particular challenges in this population are: (i) the effects of chronic arthritis and joint disease, which are accelerated by hemarthrosis; (ii) the concern of fall risk, which carries significant morbidity and mortality, even in the elderly population without hemophilia; (iii) the role of venous thromboembolism prophylaxis during and after joint replacement surgery; and (iv) the balance of managing antiplatelet and anti-coagulant therapy in patients with comorbid CVD.

Osteoporosis

Osteoporosis is an under-recognized and under-treated health problem, both in the general male population (14, 15) and in those with hemophilia (16, 17). In the general male population, one-quarter of men will experience an osteoporotic fracture, one-third of all elderly men will die within 1 year of a hip fracture, and in those with osteoporosis, the relative risk of a fracture is increased 4–5 fold (14, 15).

Accumulating evidence suggests that osteoporosis is also a frequent concomitant condition in men with hemophilia (16, 18). The risk of osteoporosis in the hemophilia population

appears to be compounded by diseases such as human immunodeficiency virus (HIV), possibly by hepatitis C virus (HCV) infection, and by the treatment of these infections. "However, we still have some way to go to identify who is at most risk in the hemophilia population, how we best assess their bone density, what is a clinical significant finding, and how we intervene both to prevent and treat osteoporosis," Prof. Konkle explained.

Cardiovascular disease

The available data on CVD in male hemophiliacs are conflicting. Previously, it was thought that hemophilia patients were protected from developing CVD. Today, however, the aging hemophilia population may have a cardiovascular risk similar to that of the general male population. Moreover, these patients may also acquire risk factors for CVD, as a consequence of advancing age. Findings from Italian Hemophilia Treatment Centers demonstrated that men with hemophilia and CVD have at least two risk factors for CVD – with obesity, hypertension, and renal disease being common risk factors. Hemophilia patients with CVD also appear to have an increased prevalence of hypertension and chronic renal disease, both of which are risk factors for CVD. Also, the CVD risk is compounded further by HIV and HCV infections in the aging population. Whether chronic inflammation associated with joint hemorrhage impacts atherosclerotic vascular disease remains unclear.

Treatment of CVD in the male hemophilia population remains a challenge. The balance between the risk of bleeding and that of thrombosis requires careful evaluation. Data for guiding the management of these patients remain scarce (13, 17).

Liver disease

As Prof. Konkle explained, HCV infection is the major cause of liver disease, liver failure, and liver transplantation, and is the leading cause of death in patients with hemophilia from countries where contaminated blood products were infused (see reviews [13, 19]). HCV and HIV co-infection accelerates the progression to liver cirrhosis and failure. A common cause of mortality in the aging hemophilia patient is hepatocellular carcinoma, the risk of which increases with advancing age and older age at the time of HCV infection. "While there is some evidence that mortality from hepatocellular carcinoma is decreasing, perhaps from more aggressive treatment and, potentially increased surveillance, we certainly need better screening and treatment," said Prof. Konkle.

Renal and urological disease

There is an increased risk of renal problems, particularly acute and chronic renal failure, in the aging hemophilia population. Several risk factors for renal disease have been identified, including HIV infection, hypertension in both acute and chronic renal disease, and recent admission for renal bleeding in chronic renal disease. Hematuria is a frequent manifestation of renal bleeding in patients with hemophilia. In older men, hematuria may also be a presenting symptom of benign prostatic hypertrophy. Optimal evaluation and treatment of hematuria is therefore paramount.

Sexual dysfunction

An important aspect of male aging is the change in sexuality, which is an under-recognized problem in the hemophilia population. Several factors have been identified that may impact male sexuality, including orthopedic disability, pain and pain medications, viral infections, decreased testosterone levels with HIV infection and/or HIV treatment, and general aging issues, such as atherosclerotic vascular disease. "One can imagine the challenge in

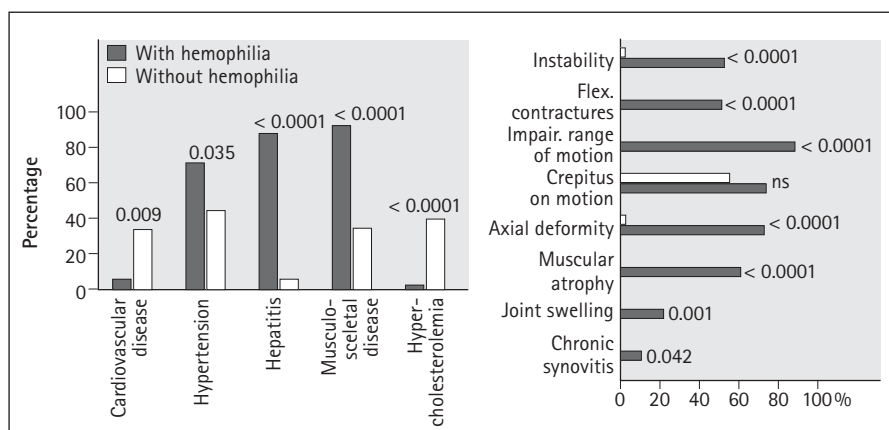


Figure 2: Health status of Italian men with and without hemophilia aged 65–78 years. Prevalence of comorbidities (left panel) and presence of alterations in the orthopedic joint score (right panel). Reproduced with permission from John Wiley and Sons, Copyright ©2009, Siboni SM, et al. Health Status and quality of life of elderly persons with severe hemophilia born before the advent of modern replacement therapy. *J Thromb Haemost* 2009; 7: 780–786.

this population and I am sure that we are not meeting it as we should – certainly more education and information are needed,” explained Prof. Konkle.

Health-maintenance issues

Comprehensive health maintenance screening for the aging male hemophilia population is becoming an important part of their primary care. However, certain precautionary procedures, such as colonoscopy or prostate biopsy, may be delayed in patients with hemophilia, owing to the inherent bleeding risks. Ideally, hemophilia maintenance care should include a network of healthcare professionals to address the many different challenges of the aging hemophilia population. In doing so, age-related problems can be identified, prevented, and/or treated earlier. “Having said that, we are still lacking evidence-based recommendations on how best to do this,” commented Prof. Konkle. We need to find the best approaches to prevent morbidity with aging, including the role of continued prophylaxis and the promotion of healthy lifestyles to control and prevent risk factors for disease.

Prophylaxis in bleeding disorders

Prophylactic therapy of hemophilia is effective in preventing bleeding episodes, reducing long-term morbidity, and improving physical activity and quality of life. Based on the long-term clinical experience from countries, such as Sweden and Germany, prophylaxis is now considered optimal therapy for patients with severe hemophilia. However, several unresolved challenges remain, and, as such, are the subject of ongoing clinical investigation. Prof. Johannes Oldenburg from the University Clinic Bonn, Bonn, Germany, highlighted key clinical data on the prophylaxis of bleeding disorders and summarized the findings from his own clinical experience.

Prophylaxis of rare bleeding disorders

Patients with rare bleeding disorders, such as rare factor deficiencies (e.g. fibrinogen deficiency), have variable bleeding manifestations that may be severe and/or linked to intracranial

bleeding, which is a significant cause of mortality. Hemarthrosis is usually rare, but epistaxis, menorrhagia, and soft tissue or mucosal bleeds typically predominate. Safe clotting factor products are available for the home treatment of rare bleeding disorders. Unfortunately, there are no comprehensive studies of patients with rare bleeding disorders – most of the available data come from case reports and treatment is based on individual clinical bleeding phenotypes. “But we know that a severe clinical course of disease with such deficiency clearly benefits from prophylaxis. It is, however, always an individual decision as to which patient to put on prophylaxis,” said Prof. Oldenburg.

Prophylaxis – When to start? When to stop?

In the setting of hemophilia, the consensus is that prophylaxis should start early in life, before the onset of joint disease. This recommendation is supported by results from the study of Manco-Johnson et al. (20), who impressively demonstrated the benefits of prophylaxis in preventing joint bleeds and damage in young children with hemophilia (20). While the benefits of primary prophylaxis are well documented, data regarding secondary prophylaxis are limited, particularly in adolescents and adults. Thus, there is currently no consensus as to when to stop prophylaxis, if at all, or if it should be tailored to individual patients, according to their clinical course. The cost of prophylaxis in adult patients is not necessarily more expensive than that in children. Consider-

ing the pharmacokinetics and the dose of FVIII used for prophylaxis in hemophilia patients, both the in vivo recovery and half-life are shorter, and the required dose per kg per year is higher in children than in adults (21). “So prophylaxis in adults might be a tailored treatment with individual patient assessment of dosage and intervals that lead to a reduction of costs without influencing quality of life,” explained Prof. Oldenburg.

The outcome of tailoring prophylaxis in adult patients has been demonstrated in a cohort study of the effect of discontinuing prophylactic therapy in patients with severe hemophilia (22). In that study, a prognostic score was developed to predict the success of stopping prophylaxis. The score was developed, based on the frequency of bleeds and factor concentrate consumption in the past. Patients with a low prognostic score had a high predicted probability, and were therefore able to stop prophylaxis and switch to on-demand therapy, with a good clinical outcome (► Fig. 3). Conversely, those with a high prognostic score had a low predicted probability of stopping prophylaxis successfully, and therefore continued with a prophylactic regimen. “This study clearly shows that prophylaxis in adults can be tailored individually,” said Prof. Oldenburg.

Prophylaxis in VWD

Compared with hemophilia, there are not many clinical data on prophylaxis in VWD. Current data suggest that secondary prophylaxis may be beneficial for patients with type 3 disease

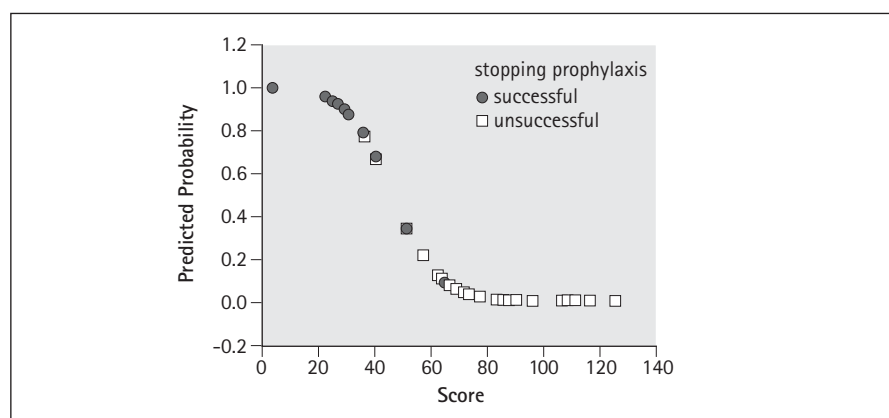


Figure 3: Predicted probability of successfully stopping prophylaxis according to the calculated prognostic score. Reproduced with permission from John Wiley and Sons, Copyright ©2001, Fischer K et al. Discontinuation of prophylactic therapy in severe haemophilia: incidence and effects on outcome. *Haemophilia* 2001; 7: 544–550.

and for certain patients with type 1 or type 2 VWD (23). The most common indications for VWD prophylaxis include joint bleeding, epistaxis, gastrointestinal (GI) bleeding, and menorrhagia.

Clinical experience from the Bonn Hemophilia Center suggests that prophylaxis in VWD patients has been individualized with regard to the requirement, dose, and frequency of factor replacement concentrate. A cohort of 24 patients with type 3 VWD has been followed; 15 patients received prophylactic therapy and nine patients received on-demand treatment with Haemate P. The dose for prophylaxis ranged from 12 to 350 U/kg body weight per week, reflecting the wide range and individualization of treatment. "For severe type 3 VWD, the message is that the prophylactic regimen is much more individualized than for example severe hemophilia A," said Prof. Oldenburg. Indications for prophylaxis in this cohort included mucosal bleedings, especially GI bleeding and joint arthropathy. Prophylactic therapy proved to be very effective in reducing the number of bleeds compared with on-demand treatment.

To further explore the utility and optimal approach of long-term prophylaxis in patients with clinically severe VWD, the VWD Prophylaxis Network has established the von Willebrand Disease International Prophylaxis (VIP) trial (NCT00557908). The trial is an investigator-initiated study sponsored through an unrestricted grant by CSL Behring. The primary aims of the trial are to examine the effect of prophylaxis on bleeding frequency and to establish optimal treatment regimens for the most common bleeding indications of VWD, including joint bleeding, epistaxis, GI bleeding, and menorrhagia. Prospective and retrospective data will be collected from approximately 200 patients receiving prophylaxis with any VWF/FVIII product. The prospective part of the trial is a non-randomized, multicenter study. The two retrospective studies are being conducted in parallel to examine: (i) the effects of prophylaxis on bleeding frequency; and (ii) the natural history of GI bleeding.

Conclusions

Significant progress has been made in the development and innovation of therapies for the treatment of bleeding disorders. Ongoing re-

search with novel albumin fusion proteins such as the half-life extended rFIX fusion protein (rIX-FP) is an exciting example of a promising innovation for patients with hemophilia. Furthermore, the ongoing SWIFT program broadens CSL Behring's range of pioneering biotherapies for improving the quality of life of patients with bleeding disorders. While the goals of hemophilia treatment focus primarily on preventing bleed frequency, joint disease, and other morbidities of bleeding disorders, little attention is given to patients' HRQoL, which is an important component of overall health. The ongoing Helixate® youth Quality-of-Life (HyQoL) studies aim to specifically assess HRQoL in young patients with moderate or severe hemophilia A.

The development of inhibitory antibodies is still one of the most serious and costly complications of hemophilia. ITI is the optimal treatment for eradication of inhibitors, particularly in those with a low inhibitor titer <10 BU/ml at the start of ITI and a peak historical titer <200 BU/ml, but questions still remain concerning the most effective regimen. High-dose ITI appears to achieve tolerance more rapidly than low-dose ITI; an important aspect when considering the recently communicated results of the randomized International ITI Study, which indicated a significantly increased bleeding risk for patients who were treated in the low-dose arm compared with those in the high-dose arm. Some evidence suggests higher success rates with VWF-containing FVIII concentrates than with highly purified products. Several potential ITI targets and mechanisms of action have been proposed, but remain inconclusive.

A new challenge for hematologists is optimizing care for the aging hemophilia population, who often present with comorbidities associated with both hemophilia and aging. There are no evidenced-based guidelines for the management of age-related comorbidities in hemophilia patients. However, treatment needs to be individualized, particularly considering that many elderly persons require therapeutics or maintenance procedures that interfere with hemostasis or warrant more intensive coagulation therapy.

The importance of early prophylaxis in young hemophilia patients is well documented. In adults, prophylaxis may be continued, but with a more individualized regimen. VWD patients, particularly those with a more

severe phenotype, also benefit from prophylaxis. For those with rare clotting factor deficiencies, the decision to initiate prophylaxis should consider the clinical course of the patient. Evidence from clinical experience suggests that prophylaxis should begin early, before the onset of joint damage, but the question of when to stop prophylaxis probably needs to be addressed on an individual basis.

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