Bayer WFH Symposia Meeting Report

Current Challenges, Issues, and Future Perspectives on Hemophilia Care

The World Federation of Hemophilia (WFH) World Congress held in Istanbul, Turkey, in June 2008 attracted more than 4,200 participants from over 115 countries. This report summarizes two symposia held during the congress. The first, titled ‘Overcoming Challenges in Hemophilia Care’, presented promising new data regarding the frequency of factor VIII (FVIII) inhibitor formation, outcomes of prophylaxis therapy in adolescent and adult patients, and the clinical development of longer-acting recombinant FVIII (rFVIII). The other symposium, ‘Current Issues in Hemophilia Care: the Nurse’s Perspective’, explored the issues and challenges nurses face when treating patients with hemophilia. These include management of patients with inhibitors and addressing aspects of implementing prophylactic treatment.

FVIII Inhibitor Formation and Management

By many estimates, FVIII inhibitors develop in up to 30% of patients with severe hemophilia A. The formation of an inhibitor presents a significant challenge for hemostatic management and greatly increases the risk of associated morbidities. Therefore, the accurate evaluation of FVIII product immunogenicity is an important consideration from both a clinical and regulatory perspective.

Inhibitor Surveillance

Jørgen Ingerslev from Aarhus University, Denmark, discussed the importance of product safety monitoring through post-marketing surveillance studies (PMS) for a rare condition such as hemophilia. Data have recently become available from three major observation studies (PMS) for a rare condition such as hemophilia. Data have recently become available from three major observation studies (PMS) for a rare condition such as hemophilia. Data have recently become available from three major observation studies (PMS) for a rare condition such as hemophilia.

An analysis of inhibitor safety data across all rFVIII-FS studies, pre- and post-licensure, included more than 400 patients who had switched from plasma-derived FVIII (pdFVIII) to rFVIII-FS. None of these patients developed an inhibitor, suggesting that switching from pdFVIII to rFVIII is not a significant risk factor for inhibitors, a finding supported by an independent study [4]. Furthermore, no de novo inhibitor formation was observed for up to two years among 274 Canadian patients who switched to rFVIII-FS from a predecessor rFVIII product [5]. A single low-titer transient inhibitor was detected among 77 Irish patients with no known history of inhibitors, who were switched from a Chinese hamster ovary cell-derived FVIII to the baby hamster kidney cell-derived rFVIII-FS [6]. These findings suggest that switching between recombinant products is also an option for patients. Surgical intervention is an established risk factor for inhibitor development. Three cases of de novo inhibitors were detected in the combined clinical and PMS database (n > 1,691); all appeared after a surgical procedure.

The European Hemophilia Safety Surveillance (EUHASS) system has been recently formed to provide continuous surveillance of hemophilia in Europe. EUHASS will capture all serious adverse events, including inhibitor formation, for hemophilia and allied disorders.

Inhibitor Management

Kate Khair, from Great Ormond Street Hospital for Children in London, reviewed factors that have been implicated in inhibitor development including ethnicity, type of gene mutation, family history, number of exposure days, and age and intensity of treatment at first exposure. Although it was previously thought that product type might also have a role, the CANAL (Concerted Action on Neutralizing Antibodies in severe hemophilia A) study found no statistically significant difference in inhibitor development between PUPs who received pdFVIII and rFVIII [4], and clinical data for rFVIII products have been reported as low as 15% [7]. Early initiation of prophylaxis may decrease the risk of inhibitor development by 60% [4].

In patients who develop an inhibitor, bypassing agents are often used to avoid life-threatening and limb-threatening bleeds. However, the optimal treatment is usually initiation of immune tolerance therapy (ITT) to eradicate the inhibitor and thereby restore normal response to FVIII.

Treatment regimens are intensive, involving high FVIII doses administered frequently over long periods of time. ITT is expensive in the short term but can be cost-effective over the long term, especially when performed in children, who make up the majority of patients with inhibitors anyway. Management of inhibitors in adulthood is more difficult and ultimately more expensive than in childhood due to the high FVIII doses required. Adherence to the regimen must be established from the outset to minimize the risk of treatment failure. Experience at Great Ormond Street Hospital has shown that even children who have failed ITT initially can have improved quality of life following intensive treatment regimens.

One of the main challenges of inhibitor management is venous access, particularly in young children. Port-A-Caths® are practical in small children and they facilitate home treatment and high-dose ITT regimens. Arteriovenous fistulae are usually reserved as a last resort, but have the advantage of reducing the occurrence of infection. Hidden costs implicated in the use of both methods include hospitalization, general anesthesia, and complications like infection and thrombosis.

Nurses provide an important role not just for the children receiving ITT, but also for their families. They can help to improve quality of life for the whole family by helping them deal with lifestyle changes. When the child leaves hospital, consideration must be given to storage of equipment and medication at home, cost of home delivery, and the impact this will have on family members.

Investigations are ongoing into treatments including plasmapheresis, multimodality treatment, alternative bypassing agents and immune suppression with rituximab and mycophenolate mofetil. Pre-implantation di-
Prophylaxis Treatment in Hemophilia A

Evidence from decades of medical practice in countries such as Sweden have demonstrated that prophylaxis therapy significantly reduces bleeding in patients with hemophilia A compared to on-demand treatment. This research further suggested a link between bleed reduction and the slowing or prevention of hemophilic arthropathy. Recent and current clinical trials are exploring and providing definitive data on this link.

Prophylaxis in Children with Hemophilia

Brenda Riske, of the Mountain States Regional Hemophilia and Thrombosis Center in Denver, CO, USA, discussed data on the value of primary prophylaxis in hemophilia. The implementation of prophylaxis varies greatly across the world, with infrequent bleeds, venous access challenges, and cost being cited as the most common reasons for not administering prophylaxis [8].

The randomized, controlled Joint Outcome Study evaluated structural joint outcome using MRI in young children with hemophilia A treated with FVIII prophylaxis or an on-demand regimen [9]. A significantly higher proportion of patients on prophylaxis maintained joints free of damage compared to the group treated on demand. Moreover, joint damage was found in some patients who had experienced little or no clinically-recognized bleeding, suggesting that undetected minor bleeding events can result in joint damage.

Prophylaxis is now widely accepted as the most effective treatment for preventing joint bleeds in children with hemophilia. However, there remain unresolved issues, such as when therapy should be initiated and terminated and which dosage regimen should be used. Ongoing and future trials are required to address these and other questions.

Prophylaxis in Adolescents and Adults with Hemophilia

Karin Lindvall, from the University Hospital in Malmö, Sweden, presented studies in adolescent and adult patients with hemophilia that have shown that prophylaxis leads to fewer joint bleeds, fewer days lost from work or school, fewer hospital days, fewer invasive procedures, and superior orthopedic outcome compared to those receiving on-demand therapy [10]. Patients who temporarily or permanently stop prophylaxis experience an increase in the number of joint bleeds and radiological score [11].

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Secondary Prophylaxis in Adolescents and Adults

Antonio Coppola, from the Federico II University Hospital of Naples, Italy, presented in interim results from the Italian POTTER (Prophylaxis vs. On-Demand Therapy Through Economic Report) study. POTTER is an ongoing, observational, multicenter, open-label study to evaluate the clinical and pharmacoeconomic impact of long-term secondary prophylaxis (rFVIII-FS 20-30 IU/kg thrice weekly) with FVIII compared to on-demand treatment in adolescent and adult PTPs (>200 prior exposures) with severe hemophilia A (<1% FVIII:C).

The prophylaxis arm includes 27 patients (14 in the 12- to 25-year age group and 13 in the 26-55-year age group) and the on-demand arm includes 25 patients (11 aged 12-25 years and 14 aged 26-55 years). After two years of follow-up, the total number of joint bleeds and non-joint bleeds were significantly reduced in prophylaxis patients compared to patients receiving on-demand therapy in both age groups. Orthopedic joint scores were also significantly reduced in the prophylaxis arm compared to the on-demand arm, particularly in the younger subgroup. Similar trends were observed when pain was included in the analysis. In addition, patients receiving prophylaxis reported fewer work or school days lost vs. those treated on demand, particularly among the older patient group. The POTTER study is continuing to observe patients for a total of four years. The results of this study are expected to help address the issues of cost-utility and cost-effectiveness of secondary prophylaxis in adolescent and adult hemophilic patients.

Evaluating Adherence to Treatment

The outcomes of any treatment regimen, long-term prophylaxis in particular, are dependent on patient adherence to that regimen. Natalie Duncan, from the Indiana He-

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mophilia and Thrombosis Center (IHTC), presented a newly validated tool to monitor adherence to therapeutic regimens in patients with hemophilia.

Adherence evaluation methods commonly include infusions logs, surveys or interviews, pharmacy dispensation data, and proxy measures such as frequency of joint bleeds, school attendance and participation in physical activities. To maximize adherence at the IHTC, patients and their families are educated on the benefits of prophylaxis and the importance of family support and involvement before initiating treatment. The regimen is kept as simple as possible and is tailored to the individual by taking into consideration factors such as patient preference and lifestyle. Home infusions are monitored via a web-based log, which is compared to prescription and dispensation data so that anomalies can be further investigated.

To better monitor patient adherence to prophylaxis, a hemophilia regimen treatment adherence scale was developed and tested in a 20 patient pilot sample prior to testing in a larger validation sample. Questionnaire items and subscales for inclusion in the scale were selected based on Morisky’s theory, which attributes drug errors to forgetfulness, carelessness and stopping or starting medication according to symptom presence [17]. Additional indicators were included to assess the correct frequency and timing of doses, appropriate dosage, and quality of the relationship between the patient and the treatment centre. The scale was validated using pharmacy dispensation data, infusion logs and health status, as well as patient and provider perceived adherence.

A full description of the scale was recently published [18].

### Research and Development of Longer-Acting rFVIII Products

The relatively short circulatory half-life of FVIII (10–14 h) requires patients to infuse FVIII as frequently as every other day to maintain adequate protection from bleeding as part of a prophylaxis regimen. The development of longer-acting FVIII products could allow for less frequent prophylactic dosing and, hence, improved compliance with prophylactic regimens.

Georg Lemm, of Bayer HealthCare Pharmaceuticals, discussed the preclinical and clinical development of a longer-acting rFVIII-FS, BAY 79-4980, that is formulated with liposomes coated with molecules of polyethylene glycol (PEG). In a FVIII-deficient mouse bleeding model, BAY 79-4980 prolonged survival following a tail bleed compared to standard rFVIII-FS. The clinical program to date has seen treatment of 89 patients with over 150 infusions of BAY 79-4980 across five trials that have demonstrated good tolerability and an extension of the time to next bleed following a prophylaxis infusion with BAY 79-4980 compared to rFVIII-FS [19]. A phase II study of BAY 79-4980, involving 66 centers in 14 countries, is initiating and will be the largest randomized controlled trial ever conducted in hemophilia A. The double-blind study will compare once-weekly infusion of BAY 79-4980 with thrice-weekly rFVIII-FS in 250 adult and adolescent patients with severe hemophilia A.

Glenn Pierce, of Bayer HealthCare Pharmaceuticals, presented research into the direct modification of the FVIII molecule itself as a method of extending the half-life. A leading approach is the attachment of PEG to specific engineered sites on the FVIII molecule. Thirty-two potential attachment sites were identified based on the known FVIII structure and multiple variants were constructed. Constructs were tested in hemA mouse bleeding models. Comparable efficacy to FVIII-FS was observed for PEGylated FVIII constructs following an acute arterial bleed. PEGylated FVIII administered 24 to greater than 72 h prior to a bleeding injury prolonged the survival compared to rFVIII-FS. Therefore, these PEGylated FVIII constructs have the potential for use in both acute treatment and prophylaxis and have a clear pharmacokinetic mechanism of action. One PEGylated FVIII (BAY 94-9027) has been selected for clinical development, and research into further FVIII half-life improvements continues.

### References