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Kreuth III: European consensus proposals for treatment of haemophilia with coagulation factor concentrates

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Summary. This report summarizes recommendations relating to haemophilia therapy arising from discussions among experts from 36 European countries during the Kreuth III meeting in April 2013. To optimize the organization of haemophilia care nationally, it is recommended that a formal body be established in each country to include the relevant clinicians, national haemophilia patient organization, health ministry, paying authority and (if appropriate) regulatory authorities. The minimum factor VIII consumption level in a country should be 3 I.U. per capita. Decisions on whether to adopt a new product should not be based solely on cost. Prophylaxis for children with severe haemophilia is already recognized as the optimum therapy. Ongoing prophylaxis for individual adults

should also be provided when required based on clinical decision making by the clinician in consultation with the patient. Children with inhibitors who have failed, or who are not suitable for, immune tolerance therapy should be offered prophylaxis with bypassing agents. Single factor concentrates should be used as therapy wherever possible in patients with rare bleeding disorders. Orphan drug designation for a factor concentrate should not be used to hinder the development, licencing and marketing of other products for the same condition which have demonstrably different protein modification or enhancement.

Keywords: factor VIII, guidelines, haemophilia, prophylaxis, treatment

Introduction

Previous meetings of experts from across Europe were held in Wildbad Kreuth in 1999 and 2009 to draw up consensus statements as a result of discussions about the regulation, use and research relating to clotting factor concentrates for therapeutic use. It is evident from a survey of 35 countries conducted by the European Haemophilia Consortium (EHC) that these Kreuth consensus statements have significantly influenced the clinical use of clotting factors in recent years [1]. This tradition has now continued and indeed been extended with the third Wildbad Kreuth meeting held in April 2013 under the aegis of the Blood Transfusion Steering Committee of the Council of Europe (CoE), in the form of a European Symposium on

‘Optimal use of clotting factors and immunoglobulins’ [2]. This was an opportunity for nominated delegates from all CoE member and observer states, along with colleagues from the EHC and regulatory agencies (e.g. EMA and the US-FDA), to review trends in the use of coagulation factor concentrates. Participants heard a series of ‘state of the art’ presentations and then met in workshops to draw up consensus recommendations relating to research and regulatory policies concerning haemophilia therapy in Europe.

Plasma fractionation for the preparation of medicinal proteins began in the 1940s with the goal of producing an albumin concentrate suitable for treating haemorrhagic shock on the battlefield. The first generation of commercial clotting factor concentrates became available in the early 1970s. At first, the risk of transmission of hepatitis was reluctantly tolerated as the price for improved haemophilia care and improved longevity of haemophilic patients. However, methods to reduce the risk of viral transmission were introduced in the aftermath of widespread HIV transmission in the early 1980s. Products of higher purity and potency

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began to appear, further improving haemophilia treatment [3]. Recombinant clotting factors were introduced in the early 1990s and have gone through several generations. Revolutionary modified products with an extended half-life are now undergoing clinical evaluation [4].

Up until the late 1980s most efforts focused on the development of plasma fractionation technology, and in particular on measures to minimize infectious risks. However, the awareness of potential risks of blood products led also to the perception that critical use of these products would help to avoid both unjustified exposure of patients to such risks and shortages in supply. Several European initiatives have dealt with the issues of self-sufficiency and optimal use of blood and blood products [5,6]. The first Wildbad Kreuth conference in 1999 addressed, along with other issues, the optimal use of the then available plasma products in the treatment of haemophilia [7]. Among the specific recommendations were: (i) establishment of patient registries; (ii) development of a network of Comprehensive Care Centres and (iii) the general recommendation of prophylactic care for children with severe disease. These recommendations were updated at the Wildbad Kreuth Initiative II in 2009 [8], and new recommendations regarding best practice, home treatment, cost-effectiveness, genetic counselling and equitable treatment across EU member states were added. The recommendations from Kreuth I & II are widely recognized as having had an impact in improving haemophilia care across the EU [1].

Nevertheless, great variability in patient care and availability of the different concentrates persists across member states. The differences in per capita use of factor VIII are particularly striking [9]. In addition to available plasma-derived and recombinant clotting factors, several new and innovative products are in different stages of development. Some of these are expected to reach the market soon [4]. Kreuth III was designed to appraise the status quo of clotting factor concentrates and immunoglobulins and identify gaps and future needs in treatment, supply and research [2].

Objective

The aim of the publication was to report on the results of the discussions among experts from across Europe during the Kreuth III meeting regarding important issues of clotting factors and haemophilia therapy.

Blood coagulation factor concentrate issues

Several new factor VIII, IX and VIIa concentrates are under development which are essentially copies of existing products. Although the term 'biosimilars' is widely used to describe such products, the group was

not entirely satisfied with this descriptive term although no obvious and universally acceptable alternative term was agreed upon. It was recognized that these products are effectively in competition with long-acting products for enrolment of patients in clinical trials. The latter are generally more attractive for scientific reasons to both patients and physicians engaged in clinical trials. However, the group felt very strongly that biosimilars should not be ignored in favour of new long-acting products. It was also accepted that there no 'short cuts' should be taken to licence biosimilar products although there certainly is an expectation that these should be significantly less expensive than current products.

The group was enthusiastic about new long-acting factor concentrates under development on the basis of data so far, particularly for IX where fivefold extension of the half-life has been achieved. It was felt that these novel agents should be used for treatment of actual bleeds as well as for prophylaxis. At the same time, the unanimous feeling of the group was that long-acting products would not completely replace the need for current plasma-derived and recombinant concentrates. The principal perceived advantage of long-acting products is the need for fewer infusions, which would be particularly helpful in children where the need for venous access devices might be avoided. It was also felt that these novel agents could make it easier to individualize therapy and maintain higher trough levels. Perioperative management would also be easier if fewer infusions are required. Possible disadvantages include concerns about enhanced immunogenicity, thrombogenicity and allergic reactions. A particular issue where the view was taken that more data are required relates to the potential for accumulation of polyethylene glycol with repeated administration over many years. The adoption of these products will also create practical problems with regard to both assignment of potency as well as laboratory monitoring in patients. New laboratory standards will be required for assays and indeed some products may eventually be labelled in mg rather than international units. The group called for pharmaceutical companies to work with the medical community to standardize useful assays. It was accepted that these novel products will be more expensive, but if this is set too high then wide-scale adoption in clinical practice will be hindered as will reimbursement from paying authorities. There would be an expectation that the price of current products would also fall at the same time.

Resolutions of the Kreuth III meeting

During the Kreuth III meeting a Working Group of experts encompassing 36 European nations agreed on the following recommendations:

Recommendation 1: To optimize the organization of haemophilia care nationally, it is recommended that a formal body be established in each country to include the relevant clinicians, national haemophilia patient organization, health ministry, paying authority and (if appropriate) regulatory authorities.

Organization of haemophilia care is a very important aspect of the disease. The group approved the ongoing work of the European Haemophilia Network project and agreed that a certification system for Haemophilia Treatment Centers should be adopted by member states based on common criteria to improve standardization of haemophilia care and provide better access to services. The group also felt that a system of peer review for external audits should be established in the longer term.

Recommendation 2: The minimum factor VIII consumption level in a country should be 3 I.U. per capita.

It was restated that prophylaxis for children with severe haemophilia is recognized as the optimum therapy, as was made clear in recommendations from both the preceding 1999 and 2009 Kreuth I and II meetings. Another major recommendation which came out of the 2009 meeting was that the minimum factor VIII level in a country should be 2 I.U. per capita. The group voted to now raise this to 3 I.U. per capita, in the light of data of a recent survey which indicated that the lower threshold is not sufficient to guarantee access to prophylaxis in children.

Recommendation 3: Decisions on whether to adopt a new product should not be based solely on cost.

The group felt very strongly that decisions on whether to adopt any new product should not be based solely on cost, but quality as well. Consensus is required on a model for assessing cost-effectiveness, which should incorporate measurement of quality of life measurements as well as historical control data for comparison. Although national tenders have been very effective in reducing prices in some countries, it is recognized that this is not feasible in all European countries.

Recommendation 4: Prophylaxis for children with severe haemophilia is already recognized as the optimum therapy. Ongoing prophylaxis for individual adults should also be provided when required based on clinical decision making by the clinician in consultation with the patient.

There was a strong feeling that the option of ongoing prophylaxis for adults should also be considered nowadays. This is especially important for younger adults, which may otherwise lose the benefits of prophylaxis in the worst case by a single joint bleed with subsequent arthropathy and need of early joint replacement. But this is also important for older adults with comorbidities treated by drugs which increase their bleeding risk. With improved life expectancy,

comorbidities in the older haemophilia population occur more often. And this can also be important for adults with a frequent bleeding type to reduce pain, to improve quality of life and to preserve the ability to work. New challenges for treatment arise and studies are so far not available.

Recommendation 5: Children with inhibitors who have failed, or who are not suitable for, immune tolerance therapy (ITI) should be offered prophylaxis with bypassing agents.

There was also consensus that children with inhibitors who have failed ITI (or are not suitable for ITI) should be offered prophylaxis with bypassing agents. No such agreement was reached in relation to the case of adults with inhibitors, mainly since many of these will already have established joint damage. In addition, the cost of ongoing treatment in adults would be very high. More research is clearly needed in relation to the principal bypassing agents, plasma-derived activated prothrombin complex concentrate (aPCC; FEIBA[®], Baxter AG, Vienna, Austria) and recombinant-activated FVII (rFVIIa; NovoSeven[®], Novo Nordisk, Bagsvaerd, Denmark). The group felt that two areas needed particular attention: development of a validated laboratory test for monitoring therapy with bypassing agents and comparative, head-to-head clinical studies.

Recommendation 6: Single factor concentrates should be used as therapy wherever possible in patients with rare bleeding disorders.

The group reaffirmed that single factor concentrates should be used wherever possible in rare bleeding disorders. It was noted that new fibrinogen concentrates have been developed recently as well as concentrates factors V and X. High-purity and recombinant von Willebrand factor (VWF) concentrates will soon become available. Theoretical advantages over combined FVIII-VWF products include viral safety and avoidance of accumulation of FVIII (which has been implicated in the development of venous thromboembolism after repeated treatment). These new VWF products were not felt to offer clear advantages over current products in routine clinical use, with the possible exceptions of elective surgery and prophylaxis in the relatively few patients with recurrent gastrointestinal haemorrhage associated with angiodyplasia.

Recommendation 7: Orphan drug designation for a factor concentrate should not be used to hinder the development, licencing and marketing of other products for the same condition which have demonstrably different protein modification or enhancement.

It was recognized that the regulators have to follow current legislation. However, pharmaceutical companies sometimes exploit the current position by requesting this protected status to secure market exclusivity for their products. This legislation should not be used to hinder access to the choice of potential new longer

acting factor concentrates where the different methods of protein modification or enhancement utilized constitute different mechanisms of action.

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Author contributions

All authors participated in the meeting and related workshops and contributed to the drafting and review of this manuscript.

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