REVIEW ARTICLE

Therapeutic properties and safety of recombinant factor VIII and factor IX

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KEY WORDS

factor VIII, factor IX, hemophilia, plasma-derived, recombinant

ABSTRACT

Advances in hemophilia management in the 20th century enabled effective and early treatment of joint and other bleeds typical of this disease, also in a home setting. Prophylaxis became available as the optimal approach to prevent hemophilic arthropathy and improve patients' quality of life. To increase treatment safety, lyophilized plasma-derived factor VIII and IX concentrates were subjected to numerous procedures designed to decrease the risk of transmission of known and unknown pathogens. During the following years, recombinant factor VIII and factor IX preparations were developed to completely eliminate the risk. Recombinant factor concentrates were extensively studied in terms of their therapeutic properties, safety, and immunogenicity. This article reviews the current knowledge on efficacy and safety of recombinant factors VIII and IX.

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Almost 40 years had passed since in 1803 John C. Otto, a physician from Philadelphia, was the first to consider hemophilia as a separate disease entity, until the first attempts to treat bleeding with whole blood transfusions were made.[1] During the early 20th century methods for blood storage, freeze-drying, and plasma fractioning were developed, followed by cryoprecipitate production, which was introduced in Poland to treat type A hemophilia patients by Professor Stanisław Łopaciuk in 1966.[2] A crucial breakthrough in hemophilia treatment came in the 1970s, when large-scale production of highly active, lyophilized, and purified factor VIII (FVIII) concentrates was initiated. This enabled home treatment and patients became independent of long-lasting transfusions in a hospital setting. Prophylactic treatment of type A hemophilia patients, introduced by Professor Inga Maria Nilsson in the late 1950s, could become intensified and more efficient.[1,3]

It was discovered only in 1947 that hemophilia was not a homogenous disease and hemophilia B, also called Christmas disease, was first described. In the late 1960s, prothrombin complex concentrates became available. They were successfully used in the treatment of hemophilia. In the early 1990s, a purified factor IX concentrate came on the market.[1]

During the early 1970s, the first attempts to reduce the risk of hepatitis B virus (HBV) infections through plasma-derived products were made. In 1971, common plasma and blood tests for HBV surface antigen were implemented. However, shortly afterwards it was discovered that hepatitis could be caused not only by the known type A and B viruses but also by other, unknown, initially called 'non-A and non-B' viruses. In the 1980s, the population of hemophiliacs became dramatically affected by human immunodeficiency virus (HIV) epidemic.[3] Extensive

work was initiated to design a method for inactivation of viruses present in coagulation factor concentrates. As a result, as early as in 1987 all available factor VIII and IX concentrates were subjected to one method of viral inactivation or viral titer reduction, e.g. using high temperature or a solvent/detergent technique in the production process. Blood donor selection, plasma pool tests, refinement of viral diagnostic techniques, and double-check procedures for viral inactivation in coagulation factor concentrates considerably increased safety of plasma-derived therapies. However, plasma-derived concentrates still entail the risk of transmitting known and unknown pathogens.[1,3-7]

Simultaneously, studies to improve factor VIII concentrate purification procedures were conducted. The use of monoclonal antibodies in the 1990s allowed to manufacture highly purified concentrates of unusually high specific activity (factor VIII coagulant activity per 1 mg of the protein in the end product) that was much higher compared to previous concentrate generations.

A great progress in hemophilia treatment was the synthesis of coagulation factors using biotechnology. Such production is independent of the availability and continuity of plasma supplies. The sequences of factor IX and factor VIII genes were described in 1982 and 1984, respectively.[8-9] Over the next few years factor VIII production method was designed. This protein was synthesized by gene-transfected mammalian cells that were cultured using special media placed in purpose-made bioreactors. To synthesize factor VIII, one of the largest proteins obtained by means of biotechnology, Chinese hamster ovary cells or baby hamster kidney cells, whose factor VIII molecules have the same biochemical properties as human plasma-derived factor VIII, are used.[1]

Recombinant factor VIII was first used in clinical practice in 1987. During the early 1990s, in the United States two novel recombinant factor VIII concentrates were introduced to the market. Human and animal proteins (in culture medium) as well as human albumin (as the end product stabilizer) were used in the production process of both products. In an attempt to completely eliminate human and animal proteins from factor VIII production process, synthetic stabilizers were used in the following years as a substitute for human albumin. Thus, the first so-called second generation recombinant was introduced to the market in 1999, followed by another concentrate that became available a year later. However, albumin was still used in their production. It was added to cell culture media. At the time when albumin-free culture media were developed, the third generation recombinant became available in 2003. This product was completely risk-free in terms of transmitting human and animal infectious particles.[1,3,10]

Studies on the factor VIII molecule showed that the so-called B domain present in its structure was not necessary to retain factor VIII biological activity. In March 2000, a B domain-free recombinant factor VIII was introduced to the market.[10] However, it was demonstrated that the presence of B domain might affect factor VIII binding to platelets, its proteolytic activation by thrombin, and activated factor VIII (FVIIIa) inactivation by activated C protein.[11]

It took many years to generate suitable cells that would synthesize recombinant factor IX. Factor IX molecule requires complex posttranslational modifications, which cannot be made using standard cell lines. The first, and to date the only, recombinant factor IX concentrate was produced in 1999 using modified Chinese hamster ovary cells. During manufacturing of this product neither human nor animal proteins are used. It should therefore be classified as the third generation concentrate.[1]

Replacement therapy is the mainstay of hemophilia A and B treatment. Available coagulation factor concentrates, both plasma-derived and recombinant, are highly effective in the prevention and treatment of bleeding. Therapeutic safety, which depends mainly on the risk of infection with known and unknown pathogens, is what calls for a precise risk benefit ratio analysis of each therapy type and regimen. Another crucial aspect that should be considered in clinical management is a possibility that the patient's organism will produce antibodies (the so called inhibitor) neutralizing the administered factor VIII or IX products. Inhibitor development is the most serious complication in factor replacement therapy. The safety of plasma-derived and recombinant coagulation factors has been extensively studied over the last few years. Clinical trials enabled scientists to draw interesting conclusions of paramount clinical importance.

Efficacy Clinical response to coagulation factor concentrates is assessed in two populations of patients, i.e. in previously untreated patients (PUPs) and previously treated patients (PTPs). The concentrates are used in on demand treatment regimen (at the time of bleeding) or in prophylaxis. Studies on individual preparations conducted to date have confirmed high efficacy of all recombinant factor VIII products for the treatment and prevention of bleeding in both populations.[12-18] They did not differ from plasma-derived concentrates in terms of pharmacokinetics, in vivo recovery, posology, and efficacy in cessation of bleeding.

There have been much fewer studies on the use of recombinant factor IX in hemophilia B due to a smaller population of affected patients and the availability of just one therapeutic product. Differences in posttranslational modification of the factor IX molecule make in vivo recovery of the recombinant factor IX reduced by approximately 30% compared to plasma-derived concentrates.[19] Nonetheless, available data show that it effectively controls bleeding both in the PUP and

PTP populations.[19,20] Its efficacy has also been demonstrated in the prevention of bleeding and in perioperative period.[20,21]

Safety The incidence of adverse events, such as allergic reactions, reactions at the site of needle insertion, and other systemic and local symptoms, is extremely low during the use of recombinant factor VIII concentrates, and is similar to that reported for plasma-derived products.[12-18, 22] Tolerance to recombinant concentrates of all generations was high both in adults and children.

The recombinant factor IX concentrate also has a good safety profile. In hemophilia B the risk of allergic reactions after exogenous factor IX administration is higher; however, there are no data available indicating that the incidence of these reactions rises in subjects receiving a recombinant factor.[19,20] Cases of red blood cell agglutination within a syringe associated with recombinant factor IX administration were reported, which nevertheless did not result in any clinical complications.[19,23] Thrombosis, which was observed during poorly purified factor IX concentrate administration, did not occur.[19-21]

Pathogen infections transmitted through coagulation factor concentrates and their immunogenicity, i.e. the ability of the hemophilia recipient's immune system to enhance the production of anti-factor VIII and anti-factor IX antibodies, require particular comments.

Infectious agents Due to the dramatic experience of viral infection epidemic in hemophilia patients, a great deal of effort has been made over the years to ensure the highest possible safety to patients. Nowadays, plasma-derived coagulation factor concentrates are manufactured in compliance with strict rules for plasma control and collection. Moreover, advanced techniques of virus inactivation are implemented. Undoubtedly, the safety of these products is currently much greater than it used to be in the past. It has been proven that currently available plasma-derived products are free of known infectious pathogens such as HIV, HCV or HBV. Moreover, no case of transmission through plasma-derived products for any of the above viruses has been reported over the last 15 years.[3,4] However, given the fact that non-enveloped viruses are resistant to available inactivation procedures, it cannot be asserted that plasma-derived concentrates are safe in this respect. Furthermore, there are reports of emerging, not only viral, infectious pathogens, which pose a potential threat to blood product recipients.[3,4] Infections caused by some viruses may manifest following a long latency period, often lasting for many years.[4] The risk of such infections and their clinical outcome cannot be evaluated at current level of knowledge. A well-documented presence of non-enveloped parvovirus B19 in the plasma-derived concentrates,[6,24-26] which until recently has been considered relatively safe in immunocompetent patients (excluding pregnant women), may have a harmful effect on the progression of degenerative lesions in the joints of hemophilia patients, according to the latest reports.[6,26] This issue, however, requires further research. In 2005, a new virus of the same family, called parvovirus 4, was discovered. In a recently conducted clinical trial[24] this pathogen was detected in 21 out of 169 various lots of 21 concentrates containing factor VIII, factor IX or prothrombin complex factors. The virus was detected, among others, in 8.9% of the tested lots of the currently used concentrates that were subjected to viral inactivation procedures (146 lots, 13 products). Clinical relevance of infections caused by this virus remains unknown.

Recently, there has been a considerable concern about the safety of hemophilia patients in relation to the prions underlying a new variant of Creutzfeld-Jakob disease. During the 10 years since the first case of the disease was reported, it has been demonstrated that the probability of its transmission through coagulation factor concentrates is negligible. However, in light of a few cases of prion infections, transmitted through whole blood or red blood cell concentrate transfusion that have been documented in the United Kingdom, it cannot be assumed that such a threat does not exist.[3,4,15,20]

Because of safety reasons in Western European and North American countries the proportion of recombinant drugs used in hemophilia therapies has grown considerably and is still increasing.[3,6] Successive generations of these preparations were designed to completely eliminate even a hypothetical risk of human or animal infectious pathogen transmission.

First generation concentrates (containing human albumin as a stabilizer and animal proteins in culture medium) are not free of potential risk for pathogen transmission. However, the risk is much lower than in the case of plasma-derived concentrates.[6,26,27] It has been shown that there is indeed a risk of parvovirus B19 transmission through the first generation concentrates[6] but it is much lower than that observed for plasma-derived products. Moreover, in patients who took both plasma-derived and recombinant products, the percentage of parvovirus infections was considerably lower compared to those who received plasma-derived products alone (in all age groups).[26] The authors of the study concluded that the risk of parvovirus B19 infection was the same in recipients of recombinant preparations as in the control group, which comprised individuals who had never been exposed to coagulation factor concentrates.[26] No single case of parvovirus B19 transmission through recombinant coagulation factor has been documented to date.[6] Highly purified human albumin is a standard stabilizer in numerous vaccines and biotechnology medications, e.g. erythropoietin or interferon. Methods for virus inactivation in the process of albumin purification are far more effective compared to those used in the manufacturing of plasma-derived

products. Furthermore, for over half a century of albumin use no single case of viral pathogen transmission has been reported.[15,28]

The second generation concentrates are human albumin depleted and the end product is stabilized with carbohydrate compounds. The risk of transmitting pathogens of animal origin, e.g. murine or bovine, through proteins added to culture medium in the production of the first and the second generation recombinants is reduced to a minimum by means of a careful animal selection and rigorous procedures of protein purification.[29]

Third generation recombinant agents are manufactured with no contact with human and/or animal proteins, which ensures their highest safety.

Monoclonal antibodies used for factor VIII purification in biotechnological processes are derived from cell lines cultured without proteins of mammalian origin.[4] The possibility that infectious pathogens occur in cell lines that have been selected, proliferated, and used in the production of all recombinant coagulation factors for many years seems to be a purely theoretical problem. However, for safety reasons, all marketed recombinant concentrates, including the third generation, are subjected to virus elimination and inactivation during manufacturing process in order to reduce a risk of pathogen penetration into the production system.[4]

In the production of recombinant factor IX concentrate neither human nor animal plasma proteins are used.[20] Therefore, recombinant factor IX concentrate is the third generation product.[20,23]

Immunogenicity Recently, it has been suggested that recombinant concentrates might be associated with a higher incidence of inhibitor development compared to poorly purified plasma-derived concentrates rich in von Willebrand factor (vWF). The authors of an experimental study[30] suggested that the vWF presence in a concentrate might diminish its immunogenicity as vWF protects FVIII from dendritic cell endocytosis. In two retrospective studies involving previously untreated children affected by a severe form of type A hemophilia and in a systematic review of the studies on anti-FVIII inhibitor epidemiology[31-33], it has been demonstrated that incidence of autoantibody-related adverse effects might be higher for recombinant factor VIII than for plasma-derived concentrates, especially those containing vWF. On the other hand, no such correlation has been found in numerous studies on individual recombinant concentrates[12-18] and a recent retrospective, multicenter CANAL trial. A review of the available literature conducted in 1999[35] showed that after adjustment for the number of days of exposure, severity of hemophilia and the frequency of routine tests for inhibitor, incidence of inhibitor development did not differ between recombinant and plasma-derived concentrates.

Undoubtedly, the risk for FVIII inhibitor development is to the highest degree dependent on genetic factors, i.e. the severity of hemophilia, type of FVIII gene mutation, race, family history, polymorphisms of some genes associated with immune response, and some modifiers such as age at first exposure, therapeutic regimen, or concentrate doses.[31,36-38] Particular attention should be paid to a recently proven reduced risk of inhibitor in the case of early regular administration of the FVIII concentrate.[34,37,38] When results of clinical studies are interpreted, it should be taken into account that during studies on recombinant factors, frequent measurements of inhibitor titer were performed (e.g. once a quarter). This was not observed in previously conducted studies on the safety of plasma-derived concentrates. As a result, clinically irrelevant and transient inhibitors were not detected and the overall incidence of inhibitor was underestimated. Another important difference is the duration of follow-up. In the previous reports on plasma-derived factors it usually did not exceed 6 months, which further limited inhibitor detection. An adequate selection of study subjects also plays a major role in the interpretation of results, because the inhibitor-related risk is markedly lower in PTP patients.

Given the above confounding factors, the size of the study sample, and methodology, an attempt has recently been made to conduct a critical review of the available data on immunogenicity of the recombinant factor VIII. World experts in the field of hemophilia agree that immunogenicity of the various types of factor VIII concentrates still remains an unresolved problem, mainly due to a lack of properly designed clinical trials and impossibility to directly compare the results of the available studies.[3,6,39-41] At present, there is no evidence for higher immunogenicity of recombinant concentrates, while unambiguous data may only be derived from prospective, randomized clinical trials, such as the currently conducted SIPPET (Survey of Inhibitors in Plasma-Product Exposed Toddlers) study, in which mainly PUPs have been included. Its objective is to compare immunogenicity of factor VIII recombinant concentrates to plasma-derived concentrates with high vWF content.[42] The suggestion that vWF contained in poorly purified FVIII plasma-derived concentrates may have a protective role deserves special attention, and undoubtedly requires further research.

In the studies on recombinant factor IX concentrates incidence of inhibitor development was not higher than in the case of plasma-derived concentrates (1.5–3.0%).[19-21,43]

Management recommendations In many countries recombinant coagulation factors are recommended as drugs of choice in both hemophilia A and B (Spain, 2008;[44] England, 2003;[7] USA, 2006;[45] Canada, 1999[46]). A number of countries earmarked extra financial support and provided all hemophilia patients with an access to recombinant preparations to prevent infections (England,

Ireland, Denmark, Scotland, Canada). Already in 2003, recombinant factor VIII constituted 50–80% of the total use of factor VIII concentrates in most European Union countries (Sweden, Germany, the Netherlands, England, France, Belgium, Norway, Italy, Switzerland, Portugal, Austria, Greece).[44,47] Experts emphasize that in view of limited funds, PUPs should be given the priority access to recombinant concentrates, followed by HIV and HCV negative patients, HIV positive patients and finally HCV positive patients.[48]

Polish management recommendations for hereditary hemorrhagic diatheses[49] stress the safety of recombinant concentrates, and their use has been suggested to treat hemophilia A and B, especially in children and in HBV, HCV or HIV negative patients.

Summary Synthesis of coagulation factors represents a milestone that ensured safe therapy for patients and protection against blood-borne infections. The safety of recombinant coagulation factors is much higher compared to their plasma-derived counterparts, despite great progress in the production and viral inactivation methods since the first plasma-derived coagulation factor concentrates were manufactured.

The next generations of recombinant factor VIII were designed so that they would be completely free of human and animal proteins. Almost two decades of extensive studies resulted in success at the beginning of 21st century, when the third generation recombinant factor VIII and factor IX concentrates were introduced to the market. Recombinant concentrates have gained greater share on the market of factor VIII and factor IX concentrates; however, their availability in the countries other than the European Union and the North America has been limited so far for economic reasons.

Recombinant factor VIII and IX products are currently unavailable in Poland. However, given a marked tendency to lower costs of recombinant factors and the current trend in medical care to focus on the safety of therapy, which is also of great concern to Polish physicians and healthcare providers dealing with patients affected by hereditary hemorrhagic disorders, it should be expected that in the nearest future previously untreated hemophilic A and B children will receive prophylactic treatment with recombinant factor VIII and factor IX concentrates.

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CONFLICT OF INTEREST

Joanna Zdziarska took part in clinical trials and received financial support for lectures and consultations from Baxter, Bayer Shering Pharma, BPL, CSL Behring, Grifols, NovoNordisk.

Krzysztof Chojnowski took part in clinical trials and received financial support for lectures and consultations from Baxter, BPL, NovoNordisk, Octapharma, Wyeth, ZLB Behring.

Anna Klukowska took part in clinical trials and received financial support for lectures and consultations from Astra Zeneca, Baxter, Bayer Shering Pharma, CSL Behring, Grifols, NovoNordisk, Octapharma, Wyeth.

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Andrzej Mital took part in clinical trials and received financial support for lectures and consultations from Baxter, BPL, NovoNordisk.

Maria Podolak-Dawidziak received financial support for lectures and consultations from Baxter Baxter, CSL Behring, and NovoNordisk and took part in clinical trials of BPL and CSL Behring.

Jerzy Windyga took part in clinical trials and received financial support for lectures and consultations from Baxter, Bayer Shering Pharma, CSL Behring, Grifols, NovoNordisk, Octapharma, Wyeth.

Krystyna Zawilska received financial support for lectures and consultations from Baxter and NovoNordisk, and took part in clinical trials of Bayer Shering Pharma and Grifols.

Właściwości lecznicze i bezpieczeństwo stosowania rekombinowanych preparatów czynnika VIII i IX krzepnięcia

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SŁOWA KLUCZOWE

czynnik VIII, czynnik IX, hemofilia, osoczopochodny, rekombinowany

STRESZCZENIE

Postęp, jaki dokonał się w dziedzinie leczenia hemofilii w XX wieku, umożliwił skuteczne i wczesne leczenie krwawień do stawów oraz innych krwawień typowych dla tej choroby, również w warunkach domowych. Dostępne stało się leczenie profilaktyczne, które jest najskuteczniejszą metodą zapobiegania artropatii hemofilowej i w ogromnym stopniu poprawia jakość życia pacjentów. Aby zwiększyć bezpieczeństwo terapii, liofilizowane osoczopochodne koncentraty czynników krzepnięcia VIII i IX poddawano licznym procedurom mającym na celu zmniejszenie ryzyka przeniesienia znanych i nieznanych czynników zakaźnych. W kolejnych latach, z myślą o całkowitej eliminacji tego ryzyka, do leczenia hemofilii A i B wprowadzono koncentraty rekombinowane. Ich skuteczność, bezpieczeństwo oraz immunogenność były i są przedmiotem licznych badań. W pracy przedstawiono aktualny stan wiedzy na temat skuteczności i bezpieczeństwa stosowania rekombinowanych czynników krzepnięcia VIII i IX.

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