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The inhibitors – a challenge for the management of patients with hereditary haemophilia A

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Introduction. Our research strategy was aimed at evaluating the possible implication of the type of factor VIII product administered as substitution treatment to haemophilia A patients in the occurrence of inhibitors and their consequences on the management.

Methods. Scientific articles from July 2015 to July 2017 were searched using the PubMed and PubMed Central databases. The used search terms included "haemophilia A", "inhibitors", "plasma-derived factor VIII" and "recombinant factor VIII".

Results. The risk factors for inhibitors occurrence may be patients-related (genetic and nongenetic) and treatment-related. The possibility of a correlation between the increased purity of factor VIII given as substitution treatment and the occurrence of inhibitors is discussed in the light of literature data. Plasma-derived factor VIII is less immunogenic, but not entirely safe from the point of view of the possibility of transmitting biological agents. It is obvious that there is not enough plasma-derived factor VIII for the planet's needs. Recombinant factor VIII products have revolutionized the treatment of patients with haemophilia A over the past 3 decades by the disappearance of transfusion-related infections and their complications. They are safer in terms of pathogens and the new long-acting factor VIII products are based on recombinant DNA technology.

Conclusion. Plasma-derived or recombinant factor VIII products must co-exist on the market for the benefit of haemophilic patients. Future solutions could be: less immunogenic factor VIII products, nonfactor replacement strategies, or bispecific antibody that mimics the function of coagulation factor VIII.

Key words: Haemophilia A, Inhibitors, Neutralizing alloantibodies, Plasma-derived factor VIII, Recombinant factor VIII.

INTRODUCTION

Haemophilia A is an inherited disease with an X-linked pattern. The plasma level of functional clotting factor VIII is low or absent. It is estimated that its prevalence varies between 1/5,000 and 1/10,000 men [1]. About 600,000 subjects suffer from haemophilia worldwide [2]. It is estimated that about 20-30% of haemophilic patients develop alloantibodies that neutralize the deficient factor (inhibitors) [2-4], a fact associated with higher morbidity [4]. Indeed, 29.3% of 147 patients with haemophilia A developed inhibitors over a 4-year period in Saudi Arabia; most of them were treated on demand (when bleeding appeared), and inhibitors occurred particularly in those with severe haemophilia (90.9%) [5]. There are authors who consider that about 20-30% of those with a severe type of haemophilia A may develop an inhibitor [1]. Inhibitors can be detected during the regular monitoring or when patients no longer respond to the substitution treatment. They can be present in low [< 5 Bethesda Units/mL (BU/mL)] or high titer (≥ 5BU/mL). Transient inhibitors may be sometimes detected; they are present in low titer, can spontaneously disappear, and have no significant impact on the treatment [6]. The occurrence of inhibitors (and especially of those with high titre) is the most severe complication of these patients. The common substitution with factor VIII products is no longer effective in patients who have high and persistent inhibitor titers. Their treatment is a challenge for haematologist and much more expensive [5, 7]. The life expectancy of patients with mild or moderate haemophilia is equal to that of non-haemophilic subjects. But the occurrence of inhibitors may cause severe haemorrhages that may contribute to an unfavourable outcome. A retrospective cohort study was accomplished in 34 Australian and European centres and included 2709 patients with mild or moderate haemophilia, including 107 with inhibitors. Sixteen patients with inhibitors died at a

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median age of 71 years during a 31-year follow-up; 7 of them – due to important bleeding. The all-cause mortality rate was over 5 times higher in patients with inhibitors than in those without inhibitors [8].

Haemophilia benefits now from the most effective and safe treatment among many single-gene hereditary disorders, due to the therapeutic advances made over the past decades [9].

Our research strategy was aimed at evaluating the possible implication of the type of factor VIII product administered as substitution treatment to haemophilia A patients in the occurrence of inhibitors and their consequences on the management. Scientific articles written in English from July 2015 to July 2017 were searched using the PubMed and PubMed Central databases. All searches were up to date as of July 2017. The used search terms included "haemophilia A", "inhibitors", "plasma-derived factor VIII" and "recombinant factor VIII". Only English language papers were reviewed.

THE INCIDENCE OF INHIBITORS

Many studies observed an increase in the incidence of inhibitors in previously untreated patients with severe haemophilia A after the occurrence of recombinant factor VIII products [10]. Some researchers have found that this increase is due to a better detection of inhibitors, others – that it is favoured by the use of recombinant factor VIII. The evolution of the incidence of inhibitors was analyzed in a large cohort of unselected previously untreated patients (926) with a severe form of haemophilia A, from 31 centres across 16 countries over 20 years (between 1990 and 2009). Its total cumulative incidence was 27.5 % and it had an increasing curve between 1990 and 2009. The incidence of low-titre inhibitors was 3.1% for the first 5 years and 10.5% over the last 5 years of study, but the incidence of those with high titers was stable throughout the follow-up period. It should be noted that screening for the detection of inhibitors has been done more and more frequently over time [10], but there are differences between centres in this regard. So, the higher incidence of low-titer inhibitors in big than in small haemophilic centres is explained at least by the more frequent testing of their occurrence. The incidence of patients with high-titer inhibitors did not significantly vary between the two types of analyzed centres [11].

Haemophilia is a rare disease, so it is not easy to carry out extensive epidemiological studies. That is why the initiative and the results of a vast European study recently carried out must be appreciated. So, European Haemophilia Safety Surveillance study included 7,969 patients with non-severe haemophilia A of 68 centres. Only 37 patients developed inhibitors during 8,622 treatment years. The incidence rate of inhibitors was 0.43/ 100 treatment years. They tended to appear at a median age of 35, after a median of 38 exposure days. They appeared more frequently at the start of the exposure (72% in the first 50 days of exposure) but have continued to appear in parallel with increasing exposure to factor VIII products [12]. Ten percent of 83 paediatric patients with haemophilia A from a single unit developed inhibitors during a follow-up period of 17 years [13]. Their incidence is three times higher than in previously treated patients with severe disease [12]. The experience of the Czech National Haemophilia Program registry between 2003-2013: none of the 45 previously untreated patients with moderate or mild haemophilia A treated on demand with recombinant factor VIII developed inhibitors. A percentage of 22.7% of the 22 previously untreated patients with severe haemophilia A treated prophylactically developed inhibitors (all in the first 50 exposure days) [14].

FACTORS THAT INFLUENCE THE OCCURRENCE OF INHIBITORS

Many factors related to the patient and the administered factor VIII product may be involved in the occurrence of inhibitors. Thus, the high dose of factor VIII, the treatment initiation before the age of 3 months, and the presence of F8 gene mutations (known as risk factors for the occurrence of inhibitors) had a significant risk for their occurrence in high titer in a multivariate analysis performed in a group of 288 children, of which 24.7% developed such inhibitors [15]. In addition, the following genetic risk factors can be added: the presence of inhibitors in the family history, the ethnic group, and certain polymorphisms in immuno-regulatory genes; the non-genetic factors that may also be involved are: young age, vaccinations, infections, trauma or surgery [16-18]. A risk score for inhibitor occurrence at the first treatment was developed by studying 332 children with severe haemophilia A. It included: the presence of haemophilia in their family history (2 points), an intensive initial episode of treatment (3 points), and the presence of high risk factor VIII gene mutations (2 points). The incidence of inhibitors varied in the studied group between 6% (in the absence of any risk factor) and 57% (at $\geq$ 3 points) [19].

THE DOSE OF FACTOR VIII

The role of the high dose of administered factor VIII is also supported by a large metaanalysis which included 761 previously untreated patients with moderate or severe form of haemophilia A from 10 centres. The patents who were treated with a dose of factor VIII of over 150 IU/kg/week developed inhibitors in a proportion of 51%, while those who received lower doses had inhibitors less frequently (24%) [20].

THE FIRST TREATMENT PERIOD

It has been established that the highest risk of inhibitors is present within the first 20 days of exposure to the factor VIII product. Therefore, Kurnik *et al.* developed an early prophylaxis regimen with lower doses and administered less frequently to induce tolerance to the administered product in previously untreated patients [21].

FACTOR VIII GENE MUTATIONS

Mutations of the gene encoding factor VIII may be the cause of the occurrence of inhibitors. Certain factor VIII missense substitutions (as R593C in the A2 domain) are the cause of the increased incidence of inhibitors in some haemophiliac patients [22]. The P1809L missense mutation present in the A3 domain found in a mild haemophilia A patient was responsible for the conformational modification of the factor VIII molecule and for the appearance of an IgG-type inhibitor that neutralized allogeneic factor VIII [23].

THE TOLERANCE-RELATED IMMUNITY MECHANISM

Not all haemophiliac patients develop inhibitors, even if they have the same genotype or the same form of severity of the disease. This suggests the involvement of a tolerance-related immunity mechanism [24]. Some patients have mutated factor VIII, which allows a small production of the coagulation factor, and explains their central tolerance. On the contrary, only a peripheral mechanism may explain the tolerance of patients with null mutation [24].

INFLAMMATORY SIGNALS

Inflammatory signals may initiate an anti-factor VIII immune response. But it has been observed that mice intramuscularly vaccinated against influenza and then injected with multiple recombinant factor VIII doses had no higher risk to develop inhibitors; furthermore, they had a decreased immune response to factor VIII, probably through an antigenic competition [25].

ON-DEMAND THERAPY

A recently published study highlights the risks of on-demand therapy in haemophiliacs. Eighty-nine percent of the rats with haemophilia A who suffered knee joint haemorrhages produced by needle sticks and who were then treated with recombinant human factor VIII have developed inhibitors, compared to only 33% from the control group without produced haemorrhages and treated identically. This experimental study suggests that the administration of recombinant factor VIII in a patient during a haemorrhage favours the occurrence of inhibitors [26]. This occurrence was not observed in haemophilia A human patients up to now.

THE ORIGIN OF FACTOR VIII

Numerous studies have analyzed the possible role of factor VIII origin given to haemophilics as a substitute treatment in the occurrence of inhibitors. Their results are extremely different. Forty percent of those treated with recombinant factor VIII and only 22 percent of those who received plasma-derived factor VIII developed inhibitors, but the reduced sample sizes of the sub-classes did not allow to establish a clear conclusion on the role of the administered factor VIII type [20]. The European Haemophilia Safety Surveillance project studied the evolution of inhibitors in 68 centres and also found no differences in their appearance depending on the class or brand of the product [27]. But the results of the following study differ from those mentioned above; it could correlate the incidence of inhibitors with the purity of the factor VIII product. Twenty-nine percent of 377 patients, treated with various types of factor VIII products and monitored until the occurrence of inhibitors or 150 days of exposure, developed inhibitors in a cohort study. The cumulative incidence of factor VIII inhibitors increased progressively from those treated with low- and intermediate-purity plasma derived factor VIII preparations (assessed as specific activity) *versus* patients treated with high purity plasma-derived and recombinant factor VIII preparations. A higher degree of factor VIII purity increased the incidence of inhibitors regardless of the presence of other risk factors [28]. Indeed, recombinant factor VIII is suspected for a long time to be one of the causes of

inhibitors occurrence, as many epidemiological studies have revealed that it is more immunogenic than plasma derived factor VIII. This issue is the cause of a long debate among haematologists about the optimal treatment of these patients, debate which is not over. No consensus has been reached on the use of these results to optimize patient management until now. Why? The biological mechanisms that explain the differences are difficult to understand. This may be a reason [4].

THE ROLE OF VON WILLEBRAND FACTOR

Inhibitors had lower incidence in patients with pre-treated haemophilia A who received plasma-derived factor VIII plus von Willebrand factor *versus* those treated with recombinant factor VIII [29].

THE TYPE OF RECOMBINANT FACTOR VIII

Different recombinant factor VIII products may have a different risk of developing inhibitors. These differences may be related to the cell lines used for their production [30]. But the difference in the occurrence of inhibitors also exists between different studies which use the same product. Changes in clinical practice, different administration of antigen load, or patient selection bias may explain some of these differences [30].

Some studies have reported a higher incidence of inhibitors in patients treated with recombinant factor VIII products of second-generation compared to those of third-generation [11, 31, 32]. The preference of some centres to treat certain patients with certain factor VIII products was a hypothesis designed to justify the difference in the incidence of inhibitors – called "a centre effect" [11]. However, a multicentre study compared the incidence of inhibitors in patients treated in 10 large centres with that of patients managed in 18 small centres and did not find arguments for a so-called "centre effect". The influence of a positive family history of inhibitors on the choice of factor VIII product could not be tested due to the small number of patients with inhibitors in their family history existing in this study [11].

THE CHANGE OF FACTOR VIII PRODUCT

The administration of different types of factor VIII concentrated to the same patient over time has been suspected as a risk factor for the occurrence of inhibitors. A study published by Aznar *et al.* established that low titre of inhibitors and transient inhibitors occurred in 9% of patients after an average of about 323 days of exposure. This incidence was not influenced either by the number of factor VIII products used in the same patient or the change of the type of product [33]. A total of 198 changes in the factor VIII products administered to 119 patients with haemophilia A did not increase the incidence of inhibitors. Neither the change between plasma factor VIII and recombinant factor VIII increased the risk of inhibitors. Therapeutic regimens were not a risk factor for inhibitors occurrence. The age of the patient, the severity of haemophilia and associated conditions did not correlate with the occurrence of inhibitors [34].

FACTOR VIII PRODUCTS OBTAINED IN ALBUMIN-FREE CELL CULTURE

The switch of patient treatment from moroctocog alpha or other factor VIII replacement products to the new reformulated morcotocog alpha (an albumin-free cell culture product) did not result in a clinically significant increase in the risk of inhibitors [35].

OTHER TREATMENT-RELATED FACTORS

Other treatment-related factors involved in the occurrence of inhibitors may be: prophylactic treatment, continuous infusion and factor VIII extravasation [16]. The development of inhibitors may also be influenced by the peak treatment time, the number of exposure days [1], and the mode of delivery of antihaemophilic therapy (as intensity and type of treatment – prophylaxis or on demand) [36].

PARTICULARITIES OF THE IMMUNE RESPONSE

The sites in the factor VIII molecule to which autoantibodies most frequently appear can serve for the development of a new factor VIII product. Thus, an analysis using human serum albumin-factor VIII domain proteins, a technique with a detection level that is superior to homologue-scanning mutagenesis, allowed to find specific autoantibodies against A2, C1 and C2 domains of factor VIII in 23%, 78%, and 68% of 115 patients who developed acquired haemophilia A, and in 52%, 57%, and 81% of 63 patients with congenital disease. Autoantibodies against C1 domain, detected especially in patients with acquired haemophilia, are directed toward 2 crucial binding residues: 2A9 and LE2E9 [37].

The presence of antibodies against factor VIII produces therapeutic difficulties. Central tolerance to factor VIII products is also absent in patients with a hereditary absence of factor VIII. Factor VIII reactive lymphocytes are involved in peripheral tolerance mechanisms. Indoleamine 2,3-dioxygenase 1 is a key enzyme with regulatory action involved in supporting Treg function and peripheral tolerance maintenance in adult people. Tryptophan metabolites result from this enzyme activity; they prevent the production of autoantibodies against factor VIII in an experimental mouse model of haemophilia A [38].

Products containing plasma-derived factor VIII have von Willebrand factor, which protects exogenous factor VIII against uptake by antigen presenting cells and decreases the possibility of its recognition by immune effectors. But the role of von Willebrand factor in reducing the incidence of inhibitors in haemophilic patients and in achieving immune tolerance are issues still under debate [39].

The so-called "danger signals" are another cause of inhibitors occurrence, apart from the individual predisposition and the type of factor VIII product. Such "danger signals" may be an infection or surgery. It has been found that bacterial lipopolysaccharide acts synergistically with factor VIII in increasing dendritic cell activation, which has an increased expression of costimulatory molecules and a higher secretion of pro-inflammatory cytokines. CD86 expression levels on these immune cells prior to stimulation correlates with this synergistic activation. Only dendritic cells, and not other cells, can be activated by factor VIII dependently and synergistically with danger signals [40].

The response to factor VIII is T cell-dependent in haemophilia A patients. Factor VIII-specific T lymphocytes able to recognize wild-type factor VIII have been found in patients with mild/moderate disease that have some point mutations. In addition, these T cells do not recognize the mutated self factor VIII. They are involved in the increased frequency of inhibitors in these patients [41]. The suppression of the formation of inhibitors against factor VIII was experimentally obtained with oral delivery to haemophilic mice of the fusion protein between the cholera toxin and the B subunit of coagulation factor, found in chloroplasts of transgenic plants. The suppression of this immune response is a process involving regulatory T cells [42].

The regulation of anamnestic antibody responses to factor VIII in haemophilia A with inhibitors is made by the intervention of factor VIII-specific B memory lymphocytes. Ligands for toll-like receptors (especially 7 and 9) were able to inhibit factor VIII-specific memory responses when factor VIII was present in inhibitory concentrations [43]. It has been discovered that Fc gamma receptor 2B (CD32) plays a key role in regulating factor VIII-specific B lymphocytes and is involved in differentiating memory B cells into antibody secreting cells in a haemophilia A mouse model. Inhibition of CD32 by monoclonal antibodies or antigen-binding 2 fragment inhibited antibody secreting cells formation depending on the administered dose. This new therapeutic approach could contribute to a better response to factor VIII therapy in patients undergoing immune tolerance therapy [44].

Experimental studies in dogs suggest that liver-directed gene therapy can be a solution to eradicate the inhibitors [3].

IS PLASMA-DERIVED FACTOR VIII STILL A TREATMENT OPTION FOR HAEMOPHILIC PATIENTS?

Safe factor VIII concentrates did not exist at all times. For example, they have been in use in Slovakia since 1990. The experience of this country on the treatment of previously untreated patients with severe haemophilia A over the course of 25 years has been recently published. Of the 59 patients, 50 were prospectively treated with plasma-derived factor VIII and 9 with recombinant factor VIII products. Twenty-two percent of patients developed inhibitors: 14% after plasma-derived factor VIII and 67% after recombinant factor VIII products. The occurrence of inhibitors has been associated with the use of recombinant factor VIII, the presence of serious/recurrent infections within the first 50 days of exposure to factor VIII, and with a peak treatment $\geq$ 5 days of exposure to factor VIII [45]. Therefore, the incidence of inhibitors is significantly lower in patients with severe haemophilia treated with plasma-derived factor VIII, which is extremely important given the severity of the clinical course and treatment costs of many patients with inhibitors. An explanation for this difference in incidence could be that plasma-derived factor VIII is more native than recombinant factor VIII and less immunogenic, as the chaperone protein von Willebrand factor is present in higher amount and is involved in its protection against endocytosis by antigen-presenting cells [46-48]. Moreover, plasma-derived factor VIII may contain, in addition to factor VIII, some immunomodulatory proteins [46, 49].

These benefits of plasma-derived factor VIII are confirmed by some other epidemiological studies on the occurrence of inhibitors. So, a multicentre randomized trial analyzed 251 male patients with severe haemophilia A, aged < 6 years, and previously untreated with factor VIII concentrated or minimally treated with blood components. The proportion of patients treated with plasma-derived factor VIII containing von Willebrand factor who developed inhibitors was 26.8% (18.6% of them had high-titer inhibitors). Those treated with recombinant factor VIII developed inhibitors in proportion of 44.5% (28.4% of them had high-titer inhibitors). The incidence of inhibitors in patients treated with recombinant factor VIII was 87% higher compared to those treated with plasma-derived factor VIII [50]. Mannucci *et al.* also analyzed a series of observational studies and found that previously untreated patients with severe haemophilia A who received only plasma-derived factor VIII developed inhibitors in proportion of 14.5%, whereas those treated with recombinant factor VIII had an incidence of 31% [51]. The results of a reference study in this area have recently appeared. The administration of plasma-derived factor VIII containing von Willebrand factor was compared with recombinant factor VIII treatment in a single randomized trial published so far (Survey of Inhibitors in Plasma-Products Exposed Toddlers - SIPPET), that included 251 patients with haemophilia A without or with minimal previous treatment. The incidence of inhibitors was 85% higher in the group treated with recombinant factor VIII *versus* the one treated with plasma-derived factor VIII over 50 exposure days [52]. On the other hand, Fischer *et al.* established in European Haemophilia Safety Surveillance study that the incidence of inhibitors was similar in haemophiliac patients treated with plasma-derived or recombinant factor VIII, based on the analysis of 8,622 treatment years [12]. This is the largest epidemiological study in this field. His results contrasted with those of previous studies, which had fewer patients. Future multicentre studies are required for a definite conclusion on the possible implication of recombinant factor VIII in the occurrence of inhibitors.

ADVANTAGES OF USING RECOMBINANT FACTOR VIII

Most haemophilic patients were infected with hepatitis viruses when only available therapy was the transfusions with plasma or cryoprecipitate. Plasma-derived factor VIII products represent a breakthrough, and recombinant factor VIII products (appeared in the early years of the last decade of the last century) have substantially improved the viral safety of the treatment [53]. Efficient production of various commercial products of recombinant factor VIII provided the necessary amount of factor VIII for substitution treatment worldwide and helped to extend its use for prophylactic purposes [53]. The prophylactic replacement and not on-demand therapy tends to become standard therapy for haemophilics due to the availability of recombinant factor VIII products [54]. The effects of this therapy contributed to a better joint health preservation, a decreased morbidity and mortality of haemophilic patients, and an improved quality of their life [53], which also includes an easier participation in various physical activities [54].

DISADVANTAGES OF USING RECOMBINANT FACTOR VIII

The frequency of factor VIII administrations to maintain plasma factor VIII levels above 1%, difficulties in achieving reliable intravenous access [54], the low adherence to prophylaxis (sometimes) and the occurrence of alloantibodies against infused factor VIII are the main challenges of the therapy with recombinant factor VIII products [53]. Substitution with factor VIII products may cause difficulties due to the lack of immune tolerance, which leads to the formation of inhibitors [55]. But the occurrence of inhibitors is multifactorial; it depends on genetic factors (such as the factor VIII gene) and environmental factors (eg, the presence of inflammation) [4]. In addition, the process is complex, as there is a dynamic interaction between inherited and environmental factors [9].

An important way to reduce the risk of developing inhibitors is to decrease the immunogenicity of factor VIII products [4]. But how? It is not easy to answer this question, but some solutions have been found. The results of the most recent clinical trials with new recombinant products are extremely encouraging from this point of view. It would be ideal if this extremely low incidence or even the absence of risk of inhibitor occurrence (mentioned in many of these clinical trials) would be confirmed by medical practice, reflected in future observational studies or multicentre trials.

CONCLUSION

The controversy on the possible correlation between the purity of the factor VIII products

(including the recombinant ones) and the increased incidence of inhibitors is far from being solved. Clear evidence is needed, in line with evidence-based medicine practices, supported by several large clinical trials. This possible correlation is an important alarm signal for drug companies to find new, safer and more efficient technologies. At the same time, it is a lesson for the production of other biological drugs, for other pathologies.

The use of plasma or plasma-derived factor VIII that have not undergone the required viral inactivation steps conduced in the past to numerous cases of transfusion-associated virus infections (especially with hepatitis C virus or human immunodeficiency virus). But suitable methods of viral inactivation for plasma-derived factor VIII preparations are used today. However, these products are not entirely safe on the possibility of transmitting biological agents (e.g. some viruses or prions). But they are cheaper than recombinant factor VIII products.

Recombinant factor VIII products have revolutionized the treatment of patients with haemophilia A over the past 30 years by the disappearance of transfusion-related infections and their complications. Thus, haemophilic patients today have a life expectancy which now approaches that of the general population if they receive substitution treatment with such products.

Plasma-derived factor VIII is less immunogenic, but there are not enough amounts of this product for all hemophiliacs. On the other hand, recombinant factor VIII is safer in terms of pathogens and the new long-acting factor VIII products are based on recombinant DNA technology [46]. For these reasons, the two types of products must co-exist on the market for the benefit of haemophilic patients. The treatment can be personalized and the patient may be invited to choose after prior information on the benefits and disadvantages of each category of factor VIII products.

Future solutions could be the production of less immunogenic factor VIII products or the application of nonfactor replacement strategies that can bypass the inhibitor, the use of products that act by natural anticoagulant inhibition, the suppression of hepatic antithrombin production [24], or the use of a bispecific antibody to mimic the function of coagulation factor VIII [24,54].

Conflict of Interest: No conflict of interest to declare.

Introducere. *Scopul cercetării noastre a constat în evaluarea posibilelor implicații ale tipului de produs de factor VIII administrat ca tratament substitutiv pacienților cu hemofilie A privind apariția inhibitorilor şi consecințele lor asupra managementului.*

Metode. *S-au studiat articolele publicate în PubMed şi PubMed Central între iulie 2015 şi Iulie 2017. Termenii de căutare au fost „haemophilia A", „inhibitors", „plasma-derived factor VIII" şi „recombinant factor VIII".*

Rezultate. *Factorii de risc pentru apariția inhibitorilor pot fi legați de pacient (genetici şi non-genetici) şi de tratament. Posibilitatea unei corelații între puritatea crescută de factor VIII administrat ca tratament substitutiv şi apariția inhibitorilor este discutată în lumina datelor din literatură. Factorul VIII derivat plasmatic este mai puțin imunogen, dar nu este în întregime sigur din punct de vedere al posibilității de transmitere a agenților biologici. Este evident că nu există suficient factor VIII derivat plasmatic pentru necesitățile planetare. Produsele de factor VIII recombinant au revoluționat tratamentul pacienților cu hemofilie A de-a lungul ultimelor 3 decenii prin dispariția infecțiilor legate de transfuzii şi a complicațiilor lor. Ele sunt mai sigure în ceea ce priveşte posibilitatea transmiterii agenților patogeni şi noile produse de factor VIII cu durată lungă de acțiune sunt bazate pe tehnologia ADN-ului recombinant.*

Concluzie. *Produsele de factor VIII derivat plasmatic sau recombinant trebuie să coexiste pe piață pentru beneficiul pacienților hemofilici. Soluții viitoare ar*

putea fi: produse de factor VIII mai puțin imunogene, strategii care nu presupun înlocuirea factorului deficitar sau anticorpi bispecifici care mimează funcția factorului VIII al coagulării.

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