Haemophilia is considered to be the most severe coagulopathy, characterized by a deficiency either of factor VIII (haemophilia A) or coagulation factor IX (haemophilia B), presenting various degrees of severity depending on the residual factor level. Haemarthrosis is the most common clinical expression of a haemophilic patient. Its repetitive character will cause irreversible lesions in the joints, which mark the beginning of a chronic condition - haemophilic arthropathy, which slowly develops throughout the patient’s life, leading eventually to ankylosis. Over time, these joints will require total prosthesis, in order to improve locomotor activity. Achieving effective hemostasis is an essential element for the possibility of performing this type of surgery, due to the increased risk of bleeding, of a vital nature, at this category of patients. A series of clinical trials have been carried out to research the role of the Eptacog Alpha Recombinant treatment in the reduction of bleeding in haemophilic patients with present inhibitors, to whom total arthroplasty is carried out at the level of various joints. In this regard, this paper aims to highlight the effectiveness of Eptacog Alpha Recombinant in the management of haemostasis in haemophilic patients, with indication of total endoprosthesis.

Keywords: Haemophilia, Eptacog Alpha Recombinant, anti-factor VIII antibodies, total arthroplasty

Haemophilia is a constitutional haemorrhagic disease based on a common blood coagulation defect (lack of an antihemophilic globulin). It is characterized by similar clinical symptomatology and identical gene transmission (recessive and gender-related) [1]. Haemorrhagic episodes may be triggered by a mild trauma, minor surgery, intramuscular or subcutaneous injections, or may occur spontaneously, particularly in the case of severe haemophilia [1]. For every patient, the degree of severity of the disease remains unchanged throughout life, with variable clinical manifestations.

The development of alloantibodies, which neutralize the therapeutically administered coagulation factor VIII or IX, is the most severe complication related to the treatment of haemophilic patients. Factor VIII antibodies develop in approximately one-third of previously untreated haemophilic patients with severe hemophilia type A, especially in the first 10 to 15 days of the substitution treatment. The risk of developing inhibitors decreases later, becoming almost negligible in treated patients, who were exposed to factor VIII over 50-150 days. However, the risk of their occurrence never disappears. It persists for almost the entire life and displays a slight increase in the case of elderly patients. When the inhibitor level persists at a high titer, they endanger the standard substitution treatment with factor VIII or factor IX concentrate, which leads to the necessity of modifying the therapeutic behavior. It is necessary to start a treatment with a by-pass concentrate of prothrombin-activated complex (aPCC) or recombinant active Factor VII (rFVIIa), which shunts the intricate pathway of coagulation by activating its extrinsic mechanism. The secondary therapeutic response to their administration is unpredictable and it has been established that no laboratory method has been validated to monitor the efficacy and safety of the treatment. As a result, haemophilic patients with inhibitors present a much more altered articular status and quality of life compared to haemophilic patients without inhibitors, while the heredity of inhibitors by inducing immune tolerance is the therapeutic standard especially in the case of children. The mechanism responsible for the development of inhibitors has just been partially elucidated, but studies on previously untreated patients with severe haemophilia have led to the identification of a multitude of risk factors, due to genetic causes (nule mutation of the FVIII gene, genotype of the major histocompatibility complex, polymorphism of immunoregulatory genes and ethnicity) and treatment-related factors. That indicates a multifactorial pathogen resulting from the complex interaction between genetic and environmental factors [2,3]. Inhibitors are more rarely developed in patients with moderate hemophilia type A (FVIII = 1-5%) or mild forms of the disease (FVIII> 5-40%). Unlike severe forms of Haemophilia (FVIII <1%), the risk of inhibitor formation in these forms of the disease increases in parallel with the exposure to FVIII concentrates, i.e. frequently in the case of adult patients after exposure to intensive care [4, 7]. The incidence of inhibitors is also lower in the case of patients with previously untreated type B hemophilia who are frequently associated with large deletions in the F IX gene [8].

Based on the level of inhibitor titer and the occurrence of anamnestic response after reexposure to factor concentrations, inhibitors are classified as low responders
(LR, inhibitors < 5 BU/mL) and high responders (HR, inhibitors > 5 BU/mL, at one determination) at least.

Patients with low inhibitor titer (LR) usually have fewer clinical complications because haemostasis can often be achieved by satu rat ing inhibitors, administering higher doses of the deficient factor. On the contrary, in the case of patients with high inhibitor titer s, although bleeding episodes are not more common than in the case of patients without inhibitors, alternative haemostatic agents are recommended, in spite of the fact that their efficiency level and a safety profile are lower than those of factor concentrations. Thus, bleeding episodes are much more difficult to control, resulting in higher risk of morbidity, mortality and disability, with an important effect on the quality of life of patients and the cost of health care [9, 10].

For this reason, the main purpose of the treatment is the permanent eradication of inhibitors by inducing immune tolerance (ITI), with the primary goal of preventing or at least reducing the negative impact that inhibitor persistence has on morbidity and the quality of life of patients. Bypassing agents are the treatment for bleeding management in patients with high inhibitor titres. Choosing the best treatment strategy by using these bypass agents is of fundamental importance for patients who are not eligible or who have failed to benefit from ITI, in order to diminish bleeding morbidity and improving their quality of life.

Current options for bypass treatment are: activated prothrombin complex concentrate (aPCC, FEIBA) and recombinant active factor VII (rFVIIa).

Haemophilic arthropathy is the main chronic complication of this pathology and it can affect one or more joints, mainly the knees, hips, ankles and elbows, in approximately 90% of haemophilic patients. [11]. From the orthopedic perspective, treatment of haemophilic arthropathy can be carried out by conservative or surgical procedure. In cases of severe haemophilic arthropathy, it is addressed by basic surgical procedures, consisting in total arthroplasty, radiosinovectomy, chemical synovectomy, arthroscopic arthrosotomy and arthrodesis [12]. The indications for arthroplasty are: joint pain and disability, which are not responsive to conservative treatment, as well as advanced radiological modifications. The objectives of such intervention are to reduce pain, improve joint amplitude and correct deformations. Postoperative bleeding is the major complication that may occur in haemophilic patients with total arthroplasty. Taking into consideration the major bleeding risk of haemophilic patients, mainly through coagulopathy, but also through surgical intervention, most endoprostheses are programmed so as to provide the required amount of coagulation factor for the substitution treatment. Currently, standard patient care protocols advocate for the need to use a hemostatic product that achieves an effective hemostasis, once it has been administered. In this respect, the use of eptacog alfa in haemophilic patients with present inhibitors, researched in numerous studies, has proven to be safe and effective in orthopedic surgery [4].

Eptacog Alpha Recombinant

rFVIIa is produced from kidney cells of hamster chicks, which express a cloned human FVII gene. A new form of active recombinant FVII also includes L-methionine and, therefore, the product can be stored at room temperature before use [13]. rFVIIa occurs in hemostasis by activating FX directly on the thrombocyte surface, shunting thus the tenase complex [13].

The resulting increase in thrombin generation increases platelet aggregation, leads to activation of coagulation FXIII and produces a stable fibrin clot [14]. The half-life of rFVIIa is 2-3 h in adults [15].

Experimental part

Material and method

There were orthopedically assessed two patients with severe hemophilia type A (factor VIII < 1%) with inhibitors, chronic haemophilic arthropathy, algically and functionally decompensated and severe motor deficits. They presented total endoprosthesis, whereas total arthroplasty of left hip, respectively of the left knee, was performed by a complex multidisciplinary team (hematology - orthopedics - ATI). Orthopedic surgery has benefited from well-established hematological support by specialized protocols (Giagrande protocol), providing the necessary amount of coagulation factor for the substitution treatment. Concurrently, tranexamic acid (25 mg/kg of body weight) was administered intravenously at a 6-8 h interval according to the aforementioned protocol. During both, the orthopedic intervention and the postoperative period, there were monitored the patients’ blood count, the parameters of the coagulation profile, the transfusion requirements and the eventual orthopedic complications that could have appeared. The postoperative evolution of patients was very good. They bleded about 400 mL, which is similar to patients without haemophilia, i.e. the hemoglobin level did not require a transfusion therapy. Taking into consideration the normalization of the coagulation profile after the substitution treatment with recombinant eptacog alfa, anticoagulant with low molecular weight heparin (Enoxaparin) was administered to prevent thromboembolic complications. From an orthopedic point of view, the postoperative evolution of patients was favorable in both cases, with a significant reduction in the pain of hips and knees, improvement in joint functionality and implicitly an increase in the quality of life.
Results and discussions

Active recombinant VII-factor bypass agents and activated prothrombin complex concentrate represent the main therapeutic response for haemostasis management in haemophilic patients with present inhibitors. Retrospective clinical studies have demonstrated that both agents are effective, providing effective hemostasis in more than 90% of the surgical interventions, where they have been used, approximately 80% of acute bleeding episodes and their widespread use in current clinical practice [16,17], including their use in home treatment [18, 20].

A series of clinical studies have compared the efficacy of aPCC vs. rFVIIa, but one of the most representative ones, the prospective, open-label, randomized, crossover trial (FEIBA-Novoseven comparative study, FENOC), performed in 48 haemophilic patients with inhibitors, confirmed the same efficacy of both haemostatic agents [21]. The two treatments - a single dose of FEIBA-75-100 U/kg vs. two doses of rFVII-90-120 µg/kg, used alternately in two haemarthrosis episodes, demonstrated similar efficacy (approximately 80%) in the management of early haemarthrosis. 10% - 44% of patients responded more favorably to one of the products at 6 and 12 h after treatment.

In another randomized controlled trial, carried out by Young et al., the efficacy of a aPCC 75 U/kg dose was compared to the one of three doses of rFVII a-90 µg/kg (at 0, 3 and 6 h), respectively of a single dose, in bolus, of 270 µg/kg of rFVIIa in 27 haemophilic patients with inhibitors [22].

Hemostatic efficacy was evaluated using an algorithm that took into account scores of joint pain and mobility 9 hours after the start of treatment, as well as the need for additional haemostatic agents (rescue medication) during the 9-hour observation period. There was no statistical difference in mobility and pain scores. Rescue medication was also required in a small percentage of patients, who received 270 µg/kg of rFVIIa, in bolus, but no statistical differences were observed between groups of patients that received aPCC and rFVII - 3x90 µg/kg. Based on the results of the two studies, it was concluded that both products had the same efficacy in the management of haemarthroses [17].

As for the safety profile, the administration of activated factor concentrations in haemophilic patients with inhibitors has rarely been associated with thrombotic complications, including deep venous thrombosis, pulmonary embolism, disseminated intravascular coagulation and myocardial infarction [23,27]. Thrombotic risk is considered to be related to the dosages of administered bypass agents, the duration of treatment, other associated comorbidities (hepatic, cardiovascular and metabolic infections as well as active infections), prolonged bed rest and surgical interventions, which increase the likelihood of developing thrombotic events. The concomitant use of antifibrinolytic agents and thromboprophylaxis is still questionable. The reason for the concomitant use of bypass agents and tranexamic acid is that they exert a potentially synergistic effect, increasing thus the stability of the clot [28]. Transexamic acid is generally used in combination with rFVIIa, whereas it was not used in the past in combination with aPCC due to the risk of thromboembolic complications. The combination of tranexamic acid is very useful especially in the management of mucosal bleeding [29,30].

Regarding thromboprophylaxis during treatment with bypass agents, this possibility should be considered especially in the case of patients with comorbidities or associated risk factors, who are at increased risk of thrombotic complications.

The two cases of endoprosthesis performed in our Orthopedic Service confirmed the results of the studies presented above, namely that recombinant eptacog alfa, administered according to the Giangrande protocol, proved its efficacy in the management of haemostasis.

![Fig. 3 A-B. A Severe bilateral hip osteoarthritis in a 45 years old patient with type A hemophilia - severe form, with inhibitors. B. Unicemented total hip arthroplasty (ceramic on ceramic) on the left side.](image1)

![Fig. 4. A-D. A. Severe left knee osteoarthritis in a 49 years old patient with type A hemophilia with inhibitors. B. Total knee arthroplasty with rotating hinge prosthesis. C-D. Intraoperative aspects.](image2)
Conclusions
Haemophilia is an inherited coagulopathy, whose main chronic complication is haemophilic arthropathy, which leads to ankylosis and requires surgical orthopedic treatment.

In the orthopedic surgery of the haemophilic patients, recombinant alpha eptacog alfa, as a substitution haemostatic agent, has proven effective in the reduction of hemorrhaging phenomena and transfusion requirements in patients with indication of total arthroplasty, without generating thromboembolic events, as confirmed in both endoprosthesis cases at our hospital.

All these effects of recombinant alpha eptacog reduce the risk of postoperative complications and diminish the costs of medical care.

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