Moroctocog Alfa Efficacy in Hemostasis Management in A Type Hemophilia Patients with Elective Arthroplasty

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Type A haemophilia is a hereditary coagulopathy caused by coagulation factor VIII deficiency as part of the rare, life-threatening and at-risk group of diseases that has been attributed over time a life-saving substitution treatment providing to patients diagnosed with this pathology a hope for life and quality of life similar to that of healthy population. However, substitution treatment is very expensive so that nowadays globally most patients cannot benefit from proper healthcare. The quality of healthcare is dependent on the socio-economic level of each country, being decisively influenced by the power of the National Hemophilia Organizations to generate solidarity and support of decision-makers of each country. One of the bleeding manifestations specific to haemophilia is haemarthrosis. Each haemorrhagic episode causes locally a disorder that predisposes to relapse, with the onset of the main chronic complication of this condition, haemophilic arthropathy. It has a slow evolution throughout the life of the patient and generates in time severe sequelae (ankyloses) that require total arthroplasty. Effective hemostasis is the essential element for performing this type of orthopaedic surgery, due to bleeding risk that is of vital nature, in this category of patients. In this sense, this study aims to underline the efficacy of Moroctocog alfa in the management of haemostasis in haemophiliac patients with total endoprosthesis indication, aimed to reduce joint pain and improve locomotor function.

Keywords: haemophilia, Moroctocog alfa, haemarthrosis, total arthroplasty

Haemophilia is a chronic disease (requiring a substitution treatment with life-defective factor), with different degrees of severity depending on the residual factor level. It is a rare disorder, its frequency in the population is around 100/1 million inhabitants, haemophilia A being 5-6 times more frequent than haemophilia B. What is typical for this condition is that it affects in a symptomatic manner only on male patients. The defining sign of the disease is excessive bleeding, frequently installed spontaneously or after minimal trauma, having no tendency to stop. The main treatment in patients with type A haemophilia is the substitution treatment, with plasma derivatives or recombinants coagulation factor VIII**.** Compared to total plasma, the administration of Factor VIII plasma concentrates showed better clinical results in patients with Type A haemophilia. However, their use has been associated with viral transmission such as hepatitis B, C or HIV, and has led in clinical practice to the use of recombinant coagulation factor concentrates associated with a much lower risk of viral infection transmission.

Permanent efforts made to improve the safety of administered products have led to the introduction of the newer generations of recombinant FVIII (rFVIII), each subsequent generation being an important step for safety of transmission of pathogens.

The first generation of rFVIII products contained human serum albumin as a stabilizer of the final formulation. [1] Albumin was eliminated from second-generation products, but human and/ or animal protein components were still used in cell culture processes. [2,3] In third-generation products, all human and animal-derived exogenous proteins were removed from the whole process, except for murine monoclonal antibodies, which continued to be used for immunoaffinity purification of rFVIII [4].

Between 1980 and 1985, in vitro studies demonstrated that the elimination of the middle portion (domain B) of the wild-type FVIII protein had no detrimental effect on its procoagulant activity. In vivo tests in haemophilic dogs showed that pharmacokinetic parameters remained unchanged compared to full-length protein [5]. This finding was at the basis of the discovery of recombinant FVIII with B domain deletion (BDDrFVIII), Morocactoc alfa (ReFacto®).

In terms of pharmacokinetic studies, Di Paola et al. compared the pharmacokinetic features of Morocactoc alfa with full length rFVIII (FLvFVIII, octocog alfa, Advate, Baxter) [6]. Eighteen patients with severe A-hemophilia, aged 18 to 72 years were enrolled in the study, of which 17 were included in the pharmacokinetic analysis. The results of the pharmacokinetic evaluation of the two products, using the chromogenic substrate test, demonstrated bioequivalence between moroctocog alfa and octocog alfa.

Haemophilic arthropathy, the main chronic complication of this pathology, can affect one or more joints, mainly the knee, hip, ankle and elbow, in about 90% of haemophiliac patients [7]. From the orthopaedic perspective, the treatment of haemophiliac arthropathy can be done by conservative or surgical procedure. In cases of severe haemophiliac arthropathy, it is treated by basic surgical procedures, such as total arthroplasty, radiosinovectomy, chemical synovectomy, arthroscopic arthrosctomy and arthrodesis [8]. Indications for arthroplasty are: pain and joint disability, not responsive to conservative treatment, as well as advanced radiological

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changes. The objectives of this intervention are to reduce pain, improve joint amplitude and correct deformation. Postoperative bleeding is the major complication that may occur in the haemophiliac patient who has had total arthroplasty. Considering major bleeding risk of a haemophiliac patient, mainly by coagulopathy but also due to surgery, most of the endoprostheses are aimed to provide the required amount of coagulation factor for the substitution treatment. Currently, standard patient care protocols sustain the need for using a haemostatic product, so once administered it could achieve effective haemostasis. In this regard, the use of Moroctocog alfa in patients with type A haemophilia, studied in many studies, has proven its safety and effectiveness in orthopaedic surgery [9].

Moroctocog alfa

ReFacto® contains recombinant coagulation factor VIII with B-domain deletion (moroctocog alfa). This is a glycoprotein with a molecular weight of about 170000 Da, made of 1438 amino acids. ReFacto has functional characteristics comparable to those of endogenous factor VIII. After the infusion into a haemophiliac patient, factor VIII binds to the von Willebrand factor present in the patient's blood. Activated Factor VIII operates as a cofactor for activated IX factor, accelerating the conversion of factor X into activated factor X. Activated Factor X converts prothrombin into thrombin. Thrombin then acts to convert fibrinogen into fibrin, resulting in clot formation. After the substitution treatment, factor VIII levels increase, resulting in a temporary correction of factor VIII deficiency, and trends of bleeding episodes.

Experimental part

Material and method

Orthopedically**,** five patients with haemophilia type A were assessed, aged between 35 and 62, two with severe form (factor VIII <1%), and three with moderate form (factor VIII = 1-5 %)**,** decompensated algesically and functionally chronic knee arthropathies; indicated total endoprothsis and total knee arthroplasties were performed by a complex multidisciplinary team (haematology - orthopaedics - ATI). Orthopaedic surgery benefitted from a well-established haematological support through the national specialty protocol, being provided the necessary amount of coagulation factor for substitution treatment. Both during orthopaedic intervention, and in the postoperative period, there were monitored patients' blood count, parameters of the coagulation profile, transfusion requirements, as well as potential orthopaedic complications that could have appeared. The postoperative progression of patients was very good, their bleeding, was similar to patients without haemophilia, with the exception of one patient whose bleeding was prolonged due to association and a coagulation factor VII deficiency, so that haemoglobin levels required administration a red blood cell unit. Due to normalization of the clotting profile after Morocactoc alfa substitution treatment, anticoagulation with low molecular weight heparin (Enoxaparin) was administered to prevent thromboembolic complications. It should be noted that the severity of bleeding did not correlate with the residual factor level, there were no significant differences between severe and moderate haemophilia in the amount of blood collected during the postoperative period. Also, patients aged 50-62 had a postoperative progression similar to younger patients with endoprostheses, with significant reduction in prosthetic joint pain, improved joint function, and implicitly with increased quality of life, older age not being an obstacle for such complex surgical interventions.

Results and discussions

A series of studies have assessed the efficacy of Moroctocog alfa in haemophiliac patients who have undergone orthopaedic surgeries.

A retrospective study by Steltjes et al. [10] evaluated the haemostatic effect of continuous perfusion with Moroctocog alfa in patients with type A hemophilia who had surgery requiring more than five consecutive days of treatment. The study enrolled 16 patients from eight centers who underwent a total of 20 surgeries. The haemostatic result was rated as excellent or good in 75% of interventions. In cases where hemostatic efficacy was moderate, patients underwent surgical procedures at increased risk of bleeding (removing or replacing a prosthesis, total knee arthroplasty, multiple interventions on the same joint). However, in these cases, the bleeding level was generally similar in quantity to non-haemophilic patients, consistent with the type of performed intervention.

Two postmarketing surveillance studies confirmed the data published by Courter et al. [11,12].

60 patients were enrolled in an open-label, multicenter postmarketing surveillance study by Smith et al. [11] Surgical prophylaxis was evaluated in seven patients who underwent elective surgery. Most patients were diagnosed with severe haemophilia type A haemostasis. Haemostasis was performed in all seven surgical cases of Moroctocog alfa, and resulted in an excellent or good response in each case.

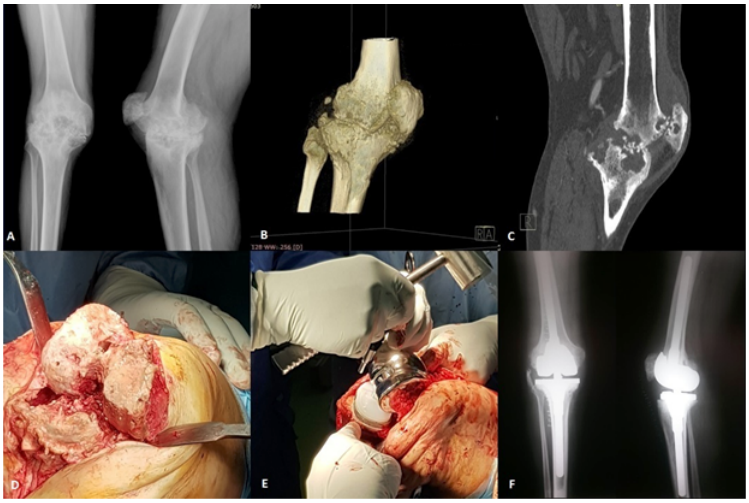

Fig.1 Total knee arthroplasty for a severe haemophilic osteoarthritis, using a modular revision rotating- hinge prosthesis

Concerning the analysis of adverse effects, the risk of developing inhibitors has been investigated by Gringeri et al [13].

A cohort of 25 cases of severe haemophilia cases who have received other types of coagulation FVIII products than Morocactog alfa has been analyzed for more than 50 days; afterwards, more than one Morocactog alfa daily was administered. The results of the study revealed the same inhibitor level as in the case of other coagulation FVIII products [13]

Concerning the safety profile, administration of recombinant factor VIII concentrates in haemophiliac patients has rarely been associated with thrombotic complications - including deep venous thrombosis, pulmonary embolism, disseminated intravascular coagulation, and myocardial infarction. It is believed that the thrombotic risk is related to doses of administered factor agents, treatment duration, and existence of other associated comorbidities (liver, cardiovascular, metabolic, active infections), the prolonged bed and surgical interventions, which increase the probability of development of thrombotic events. Applying at the same time thromboprophylaxis with heparins of low molecular weight, avoids the occurrence of thrombotic events.

The five cases of endoprosthesis performed in the Orthopedics Clinic of St. Spiridon Hospital confirmed the results of the previous studies, Moroctocog alfa, administered according to the National Hemophilia Protocol, proved its efficacy in the management of haemostasis in patients with type A haemophilia.

Conclusions

The efficacy of ReFacto has been extensively studied in numerous studies, and its efficacy and safety profile have been clearly demonstrated.

In accordance with the results of studies, in on-demand therapy, its efficacy rate was 98%, and for haemophiliac patients undergoing surgery 92%, the number of bleeds per patient/year for prophylactically treated patients was 5. 5% [14-17], and the inhibitor development rate was 6%.

There is currently no evidence of greater immunogenicity for the moroctocog alfa molecule compared to octocog alfa, or other factor VIII concentrates. In vitro and ex vivo experiments, which formulated a hypothesis of a greater neo-antigenicity of the molecule [18] was not confirmed by clinical data [19-22].

In orthopedic surgery of the hemophiliac patient, Morocactog alfa as a hemostatic substitution agent has proven its efficacy in managing haemostasis in patients with total arthroplasty, as confirmed by the five endoprosthetic cases in our hospital.

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