The Efficiency of Substitutive Treatment with Moroctocog Alfa in Managing Hemostasis in Patients with Hemophilia A Without Inhibitors With Total Knee Arthroplasties

OANA VIOLA BADULESCU[1], MANUELA CIOCOIU[1]*, NINA FILIP[2]*, VLAD VERINGA[3]

[1]Grigore T. Popa University of Medicine and Pharmacy, Faculty of Medicine, Department of Pathophysiology, Morfo-Functional Sciences (II), 16 Universitatii Str., 700115, Iasi, Romania

[2]Grigore T. Popa University of Medicine and Pharmacy, Faculty Of Medicine, Department of Biochemistry, Morpho-functional Sciences (II), 16 Universitatii Str., 700115, Iasi, Romania

[3]Grigore T. Popa University of Medicine and Pharmacy, Faculty of Medicine, Department of Orthopedics and Traumatology, Surgical Sciences (II), 16 Universitatii Str., 700115, Iasi, Romania

Hemophilia A is a hereditary coagulopathy caused by the deficiency of the coagulation factor VIII, whose main complication consists in disabling arthropathy. The most often affected joint is the one of the knee, due to which this article aims at presenting, on one hand, the role of continuous substitutive prophylactic treatment in preventing the onset of this complication and, on the other hand, the current view of orthopedic surgery in managing the above-mentioned complication. The continuous prophylactic treatment represents the best therapeutic conduct in preventing the onset of hemophilic arthropathy, yet this aspect is limited by two important factors: inappropriate medical support, dependence on the social and economic level of every country and inappropriate adherence of the patient to this thorough treatment, which represents a challenge for a life with no bleeding. Under the circumstances imposed by an insufficient substitutive treatment or by a deficient adherence of the patient to this, recurrent hemarthrosis shall lead to cartilage destruction and synovial hypertrophy (synovitis), which will impose, in time, total endoprosthesis in order to re-establish the motor function and to improve the life quality of the hemophilic patient. The surgery of the hemophilic patient is associated with an increased risk of hemorrhage and infection and it is practiced only with substitutive hematologic support. The key to the best results is the existence of a multidisciplinary experienced team, including an orthopedist, hematologist, physical therapist.

Keywords: Hemophilia A, arthropathy, hemarthrosis, synovial hypertrophy

Hemarthrosis represents the most frequent and formidable clinical expression of a hemorrhage in a patient suffering from hemophilia (75%). Its onset takes place between 1 and 5 years; when it occurs after 10 years, it is a sign of mitigated condition. The rest of the symptoms are relapses. The trigger is always a trauma which usually goes unnoticed. The topography of the damaged joints is, in a decreasing order, the following: knees (36 %), ankle (30%), elbow (23%), hand (6%), shoulder (3%) and hip (2%). Most of the hemarthroses are monoarticular; sometimes, they can be biarticular, but in this case, symmetry is not compulsory. Relapses usually take place in the same place. Each hemorrhage articular episode brings about a disorder which predisposes to relapse: the anatomical structures are weakened, muscles are supposed to atrophy and suffer from fibrosis (articular mechanics becomes deficient), the synovial is supposed to hypertrophy and hypervascularize, becoming less hemorrhagic (vicious circle). This marks the beginning of a chronical condition; *hemophilic arthropathy*, which evolves slowly throughout life and generates severe sequelae (ankylosis). *Ex vivo* studies carried out with canine cartilage suggest that its exposure to sun for 4 days leads to the loss of matrix-type cartilage[1]. Furthermore, experimental studies have shown that after a major hemarthosis, the articulation cavity is infiltrated with a dense inflammatory infiltrator, while local tissues become brownish due to the hemosiderin deposition resulting after the erythrocyte damage [2-4]. Vascular hyperplasia takes place, leading to the emergence of brittle vases, with a tendency towards bleeding, thus creating a vicious circle: bleeding-vascular hyperplasia-bleeding. The joint surface becomes rough, pannus is formed, while the subchondral bone becomes dysmorphic. After approximately one month, the cartilage and bone erosions become obvious [5].

It was showed that affected articulation can play an important role in the mechanism of cartilage destruction in hemophilic patients [6]. Other authors concluded that the molecular modifications induced by the presence of iron in the intra-articular blood could explain the increase in the cellular proliferation from the synovial membrane (synovitis) [7-9]. Valentino et al. [10] showed, in an experimental pattern, that the hemorrhage produced by a controlled trauma leads to joint swelling, synovitis and hemophilic arthropathy.

To prevent these complications, regular substitutive therapy with deficient coagulation factor applied from a young age (primary prophylaxis) represents the best therapeutic conduct in order to prevent the onset of synovitis and hemophilic arthropathy. Nevertheless, despite primary prophylaxis, some patients present intra-articular bleeding, due to an insufficient dose of coagulation factor or a deficient adherence to the treatment, while others might show sub-clinically manifested hemarthroses.

Although the pathogenesis of hemophilic arthropathy is not fully understood [11], the idea that primary prophylaxis prevents bleeding and the onset of disabling hemophilic arthropathy is generally accepted [12,13].

Primary prophylaxis must begin as soon as possible, because even an occasional or short-time contact of blood

*email: mciocoiu2003@yahoo.com, zamosteanu_nina@yahoo.com

with the cartilage can trigger chondrocyte apoptosis, which shall finally cause hemophilic arthropathy.

Once installed, hemophilic artrhopathy can be treated by means of basic surgical procedures, including chemical radiosynovectomy, arthroscopic synovectomy, arthroscopic joint debridement and finally, total knee arthroplasty [14,15].

Moroctocog alfa

Moroctocog alfa contains the coagulation factor VIII recombined, along with the deletion of the field B. It is a glycoprotein with a molecular mass of approximately 170000 Da, functional characteristics comparable to those of the endogenous factor. The activity of factor VIII is deficient in patients suffering from hemophilia A, which requires a substitutive therapy for the prevention and treatment of hemorrhagic phenomena. The mechanism of action of coagulation factor VIII exogenous administrated consists in making a connection between this and the factor von Willebrand, which is its carrier. Following the trigger of the intrinsic mechanism of thromboplastin formation, factor VIII activated acts upon the coagulation factor IX, by activating it and facilitating the conversion of factor X in active factor X. In turn, this acts upon the prothrombin, which is transformed in thrombin. Thrombin influences the conversion of fibrogen in fibrins, leading to the clot formation. Secondary substitutive treatment, plasmatic values of the factor of coagulation VIII increase, determining a temporary correction of the factor VIII deficiency, as well as of the frequency of occurrence of the bleeding episodes.

Experimental part

Material and method

Most of the patients suffering from knee hemophilic artrhopathy present a progressive deterioration, which determines the altering of quality life of these patients secondary to intense pain. For these patients, the best therapeutic solution is total knee endoprosthesis, which leads to a considerable improvement in the pain and joint function. Intervention risks consist in the possibility of bleeding and superinfection, the rate of infection usually reaching an average of 7%.

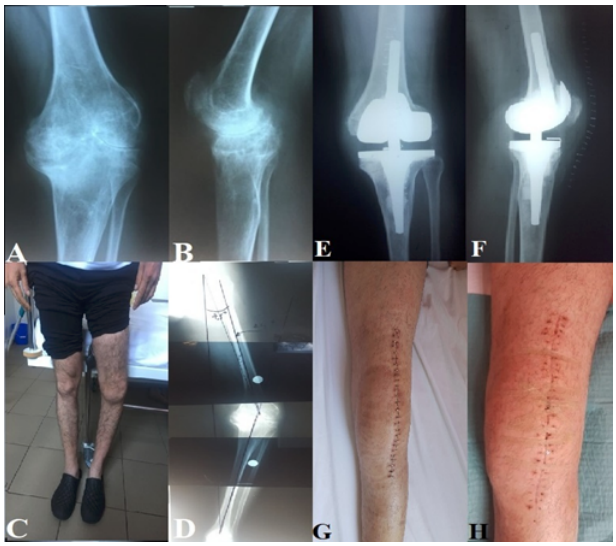

Fig. 1. A-H. Severe axial deformity. Genu varum in severe haemophilic arthropaty. A-B. Preoperative X-Rays. C-D. Severe genu-varum clinically and radiologically. E-F. Postoperative X-Rays. G-H. Clinical view of the knee with axis restored and wound healed

Five patients suffering from hemophilia A, aged between 35 and 62, two with severe form (factor VIII < 1%) and three with moderate form (factor VIII = 1-5%), with chronic knee arthropathies decompensated in terms of attenuated pain and functionality and severe motor deficit, were evaluated orthopedically. The condition of the patients required total endopsrosthesis, by means of total knee arthropathy, carried out by the complex multidisciplinary team (hematology – orthopedics – ATI). Orthopedic surgical interventions benefited from substitutive treatment with Moroctocog alfa in doses and at times established by the national expert protocol, ensuring thus the whole quantity of coagulation factor necessary to carry out the intervention. Both during the orthopedic intervention and the post-surgery period, the CBC of the patients, parameters of coagulation profile, transfusion necessary, as well as possible complication in terms of orthopedics, were monitored.

The post-surgical evolution of the patients was a very good one, their bleeding was similar to that of a patient without hemophilia, except one patient, whose bleeding was prolonged by the association with a deficit coagulation factor VII, thus the level of hemoglobin imposed the administration of an erythrocyte unit mass. Taking into consideration the normalization of the coagulation profile after the substitutive treatment with Moroctocog alfa, anticoagulant treatment with low molecular weight heparin (Enoxaparine) to prevent thromboembolic complications (except the patient associated with a deficit of factor VII). It is to be remarked that the severe bleeding was not correlated to the residual factor level, since there are no significant differences between the severe and moderate forms of hemophilia in terms of blood collected after the surgery. In addition, patients aged between 50 and 62, presented a post-surgical evolution as good as in younger patients to which endoprostheses were applied, together with a significant reduction in the pain from the joint to which prosthesis was applied, with an improvement in the joint functionality and, implicitly, life quality, since advanced age is not an obstacle in carrying out all these complex surgical interventions.

Results and discussions

A series of studies carried out assessed the efficiency of Moroctocog alfa in hemophilic patients who underwent orthopedic surgical interventions.

Smith and colab. Published data concerning 60 patients who were enrolled in a multicenter open-label study, of post-marketing surveillance who benefited from surgical interventions [16]. Surgical prophylaxis was evaluated in 7 patients who suffered an elective surgical intervention. Most of the patients were diagnosed with a severe form of hemophilia A. Hemostasis was carried out in all the surgical cases with Moroctocog alfa and led to an excellent or good response to each of the cases.

Steltjes et al. [17] evaluated the hemostatic effect of continuous perfusion with Moroctocog alfa in patients with hemophilia A subjected to a surgical intervention. The hemostatic result was evaluated as excellent or good in a percentage of 75% of all the conducted procedures. When the hemostatic efficiency was identified as moderate, patients were subjected to some surgical procedures with an increased risk of bleeding (removing or replacing a prosthesis, total knee arthroplasty multiple interventions to the same joint). Yet, in these cases, the level of bleeding was generally similar in terms of quantity to the non-hemophilic patient, according to the type of intervention carried out.

As for the possibility of emergence of side effects, the risk of inhibitors development was investigated by Gringeri and colab [18].

A cohort of 25 cases with a severe form of hemophilia who received other types of FVIII of coagulation than Moroctocog alfa, was analyzed for more than 50 days; afterwards, they received many doses of Moroctocog alfa daily. The results of the study emphasized the same rate in the level of inhibitors as in the case of administration of other FVIII products of coagulation [18].

As for the security profile, administration of factor VIII concentrates recombined in hemophilic patients was rarely associated with thrombotic complications, including deep venous thrombosis, pulmonary embolism, disseminated intravascular coagulation and heart attack. It is considered that the thrombotic risk is connected to the doses of factor agents administrated, to the treatment duration, as well as to the existence of other comorbidities (hepatic, cardiovascular, metabolic infections, the existence of active infections), prolonged stay in bed and surgical interventions, which increase the probability of thrombotic events development Carrying out the thrombophylaxis with low molecular weight heparin avoids the onset of thrombotic events.

The five cases of endoprosthesis carried out in the Orthopedics Department of the Sf. Spiridon Hospital, confirmed the results of the studies previously presented, Moroctocog alfa, administrated according to the National Hemophilia Foundation, proving its efficiency in the field of hemostasis management in patients with hemophilia A.

Conclusions

The optimum treatment for hemophilic patients is primary prophylaxis, resulting in the prevention of joint blood, onset of joint bleeding and complications. Orthopedic surgery in hemophilic patient is associated with an increased risk of hemorrhage and infection. This type of surgical intervention must be carried out in specialized centers, with appropriate hematologic support, in conformity with the national protocol. Only under these conditions, life quality of the hemophilic patients shall improve, by minimalizing the risk of associated complications. In orthopedic surgery of the hemophilic patient, Moroctocog alfa as hemostasis substitutive agent proved its efficiency in managing hemostasis in patients with indication of total arthroplasty, fact confirmed by the 5 endoprosthetic cases from our hospital.

References

1.JANSEN NW, ROOSENDAAL G, BIJLSMA JW, DEGROOT J, LAFEBER FP. Exposure of human cartilage tissue to low concentrations of blood for a short period of time leads to prolonged cartilage damage: an in vitro study. Arthritis Rheum 2007; 56: 199-207 [PMID: 17195222 DOI: 10.1002/art.22304]

2.VALENTINO LA, HAKOBYAN N. Histological changes in murine haemophilic synovitis: a quantitative grading system to assess bloodinduced synovitis. Haemophilia 2006; 12: 654-662 [PMID: 17083517 DOI: 10.1111/j.1365-2516.2006.01348.x]

3.VALENTINO LA, HAKOBYAN N, RODRIGUEZ N, HOOTS WK. Pathogenesis of haemophilic synovitis: experimental studies on bloodinduced joint damage. Haemophilia 2007; 13 Suppl 3: 10-13 [PMID: 17822515 DOI: 10.1111/j.1365-2516.2007.01534.x]

4.BARDAS, C,A,, GABRI, J,Z,, APOSTU, D,, OLTEAN-DAN, D,, TOMOAIA, G,, BENEA, H**.,** Functional Results of Different Repair Techniques for Knee Articular Cartilage Lesions. Rev. Chim.(Bucharest), **69**, no.11, 2018, p.3288-3291

5.BEREA, G,, BALAN, G,, SANDRU, V., SIRBU, P,D., In vitro Three Dimensional Scaffold-free Construct of Human Adiposederived Stem Cells in Coculture with Endothelial Cells and Fibroblasts, Rev. Chim.(Bucharest), **68**, no.6, 2017, p.1341-1344;

6.HOOIVELD MJ, ROOSENDAAL G, JACOBS KM, VIANEN ME, VAN DEN BERG HM, BIJLSMA JW, LAFEBER FP. Initiation of degenerative joint damage by experimental bleeding combined with loading of the joint: a possible mechanism of hemophilic arthropathy. Arthritis Rheum 2004; 50: 2024-2031 [PMID: 15188380 DOI: 10.1002/ art.20284]

7.HAKOBYAN N, KAZARIAN T, JABBAR AA, JABBAR KJ, VALENTINO LA. Pathobiology of hemophilic synovitis I: overexpression of mdm2 oncogene. Blood 2004; 104: 2060-2064 [PMID: 15172967 DOI: 10.1182/ blood-2003-12-4231]

8.CIUNTU, B.M., VASILUTA, C., NEGRU, R., HULTOANA, R., CIUNTU, R., GEORGESCU, S,T,O., SIRBU, P.D., AZOICAI D., Negative Pressure Therapy in the Surgical Treatment of Diabetic Foot, Rev. Chim.(Bucharest), **68**, no.7, 2017, p. 1648-1651

9.SIRBU PD, T PETREUS, FL. MUNTEANU, M. PERTEA, S. LUNCA, V. POROCH, P. BOTEZ, Clinical Experience with a Macroporous Synthetic Bone Substituite (Eurocer) in the Treatment of the Patitents with Bone Defects International Conference on Advancements of Medicine and Health Care through Technology IFMBE Proceedings, 2011, Volume 36. Part 5, 358-368, DOI: 10.1007/978-3-642-22586-4_75

10.VALENTINO LA, HAKOBYAN N, KAZARIAN T, JABBAR KJ, JABBAR AA. Experimental haemophilic synovitis: rationale and development of a murine model of human factor VIII deficiency. Haemophilia 2004; 10: 280-287 [PMID: 15086328 DOI: 10.1111/ j.1365-2516.2004.00899.x]

11.LAFEBER FP, MIOSSEC P, VALENTINO LA. Physiopathology of haemophilic arthropathy. Haemophilia 2008; 14 Suppl 4: 3-9 [PMID: 18494686 DOI: 10.1111/j.1365-2516.2008.01732.x]

12.NILSSON IM, BERNTORP E, LÖFQVIST T, PETTERSSON H. Twenty-five years' experience of prophylactic treatment in severe haemophilia A and B. J Intern Med 1992; 232: 25-32 [PMID: 1640190 DOI: 10.1111/ j.1365-2796.1992.tb00546.x]

13.MANCO-JOHNSON MJ, ABSHIRE TC, SHAPIRO AD, RISKE B, HACKER MR, KILCOYNE R, INGRAM JD, MANCO-JOHNSON ML, FUNK S, JACOBSON L, VALENTINO LA, HOOTS WK, BUCHANAN GR, DIMICHELE D, RECHT M, BROWN D, LEISSINGER C, BLEAK S, COHEN A, MATHEW P, MATSUNAGA A, MEDEIROS D, NUGENT D, THOMAS GA, THOMPSON AA, MCREDMOND K, SOUCIE JM, AUSTIN H, EVATT BL. Prophylaxis versus episodic treatment to prevent joint disease in boys with severe hemophilia. N Engl J Med 2007; 357: 535-544 [PMID: 17687129 DOI: 10.1056/NEJMoa067659]

14.HILGARTNER MW. Current treatment of hemophilic arthropathy. Curr Opin Pediatr 2002; 14: 46-49 [PMID: 11880733 DOI: 10.10 97/ 00008480-200202000-00008]

15.RODRIGUEZ-MERCHAN EC. Aspects of current management: orthopaedic surgery in haemophilia. Haemophilia 2012; 18: 8-16 [PMID: 21535324 DOI: 10.1111/j.1365-2516.2011.02544.x]

16.SMITH MP, GIANGRANDE P, POLLMAN H, LITTLEWOOD R, KOLLMER C, FEINGOLD J. A postmarketing surveillance study of the safety and efficacy of ReFacto (St Louis-derived active substance) in patients with haemophilia A. Haemophilia 11(5), 444–451, 2005.

17.STIELTJES N, ALTISENT C, AUERSWALD G et al. Continuous infusion of B-domain deleted recombinant factor VIII (ReFacto) in patients with haemophilia A undergoing surgery: clinical experience. Haemophilia 10(5), 452–458, 2004.

18.GRINGERI A, TAGLIAFERRI A, TAGARIELLO G, MORFINI M, SANTAGOSTINO E, MANNUCCI P. Efficacy and inhibitor development in previously treated patients with haemophilia A switched to a B domaindeleted recombinant factor VIII. Br.J. Haematol. 126(3), 398–404, 2004.

Manuscript received: 09.08.2018