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Professional article

Non-Factor Replacement Therapy: A New Chapter in Hemophilia A Prophylaxis

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SUMMARY

Introduction/Aim. Hemophilia A is an antihemophilic factor deficiency which requires life-long treatment. The aim of this analysis was to present the effects of prophylactic non-factor replacement therapy in ten patients with hemophilia A.
Patients and methods. This retrospective analysis was conducted on ten male patients (4 children, 1 adolescent, and 5 adults) with severe hemophilia A and a history of antihemophilic factor replacement prophylaxis, prior to the initiation of emicizumab prophylaxis. A single adult patient developed inhibitors during the course of factor replacement prophylaxis. Four adult patients had already developed hemophilic arthropathy before the initiation of non-factor replacement prophylaxis. Two adult patients received emicizumab prophylaxis every four weeks, while others received emicizumab every two weeks. After a 14-month period (average) of non-factor replacement prophylaxis, we analyzed the number of breakthrough bleeding episodes, annualized bleeding rate, involvement of target joints, adverse drug reactions, and interviewed the patients regarding their satisfaction with the non-factor replacement treatment.
Results. None of the patients on emicizumab prophylaxis experienced breakthrough bleeding or clinical worsening of the affected target joints during the period of emicizumab prophylaxis. Annualized bleeding rate was zero in all patients on emicizumab prophylaxis. No adverse drug reactions occurred in our patients during emicizumab prophylaxis. All patients reported greater treatment satisfaction compared to the replacement prophylaxis.
Conclusion. By providing safety from bleeding events and potentially the stability of the affected joints, emicizumab prophylaxis enables greater activity and increases the quality of life of treated patients.

Keywords: **hemophilia, antihemophilic factor, emicizumab, inhibitors, prophylaxis**

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INTRODUCTION

Hereditary hemophilia A is a congenital X-linked recessive antihemophilic factor (FVIII) deficiency, which almost exclusively affects the male population (1).

Antihemophilic factor deficiency causes bleeding events of various severity, which manifest in prolonged and postponed bleeding after surgery, spontaneous intraarticular and intramuscular hemorrhage, and other less frequent manifestations, potentially causing life-threatening complications if not treated properly (1, 2).

Until recently, treatment of hemophilia A was based on the prophylactic FVIII replacement therapy, with occasional on-demand treatment once bleeding events occurred, as well as preoperative and perioperative hemostatic treatment in case of elective surgery (1, 2).

However, in recent years, an innovative therapeutic approach based on the immunology insights and molecular engineering has introduced the concept of non-factor replacement prophylaxis in hemophilia A (3).

In this article, we will present the effects of emicizumab in ten patients with severe hemophilia A during the period of non-factor replacement prophylaxis.

PATIENTS AND METHODS

This retrospective analysis was conducted on ten male patients (4 children, 1 adolescent, and 5 adults) with severe hemophilia A and a history of antihemophilic factor replacement prophylaxis, prior to the initiation of emicizumab prophylaxis.

The youngest patient was 16 months old, and the oldest was 38 years old at the moment of non-factor prophylactic therapy initiation.

These ten patients are the first patients to have received non-factor replacement prophylactic treatment in the University Clinical Center Niš, Niš, Serbia. The non-factor replacement prophylaxis of adult patients was conducted under the supervision of hematologists of Hematology, Allergology and Clinical Immunology Clinic, whereas the treatment of pediatric patients was conducted under the supervision of pediatricians of the Pediatric Clinic.

The main reason for switching our patients to non-factor replacement prophylaxis was poor venous access.

A single adult patient developed inhibitors during the course of factor replacement prophylaxis.

Four adult patients had already developed hemophilic arthropathy before the initiation of non-factor replacement prophylaxis.

These patients have been receiving emicizumab prophylaxis within the past two years, with the average duration of emicizumab prophylaxis of 14 months amongst all ten patients.

Two adult patients received emicizumab prophylaxis every four weeks, while others received emicizumab every two weeks.

In order to assess non-factor replacement prophylaxis, we analyzed the number of breakthrough bleeding episodes, annualized bleeding rate, involvement of target joints, adverse drug reactions, and interviewed the patients/caregivers regarding their satisfaction with the non-factor replacement treatment during the past period of emicizumab prophylaxis.

The data regarding the number of breaktrough bleeding episodes, adverse drug reactions, and join status was collected from the medical record documentation.

The annualized bleeding rate was calculated for the period of twelve months between 01. 01. 2023. and 31. 12. 2023.

The characteristics of the patients, as well as the values of analyzed parameters, are presented in Table 1.

RESULTS

None of the patients on emicizumab prophylaxis experienced breakthrough bleeding or clinical worsening of the affected target joints in the period of non-factor prophylaxis. The annualized bleeding rate was zero in all patients on emicizumab prophylaxis. No adverse drug reactions occurred in our patients during emicizumab prophylaxis. All patients reported greater treatment satisfaction compared to the replacement prophylaxis (Table 1).

Table 1. *Patient characteristics and parameters analyzed during non-replacement therapy*

Parameter:	**N = 10**
Patient age groups n (%)	
children (0 - 11 years)	4 (40)
adolescents (12 - 17 years)	1 (10)
adults (18 - 64 years)	5 (50)
Average age at hemophilia screening (years)	19.16
Hemophilic arthropathy prior to emicizumab prophylaxis n (%)	4 (40)
Presence of inhibitors n (%)	1 (10)
Average duration of emicizumab prophylaxis (months)	14
Dosing regimen n (%)	
3 mg/kg Q2W	8 (80)
6 mg/kg Q4W	2 (20)
Patients without spontaneous bleeding events n (%)	10 (100)
Median annualized bleeding rate	0.0
Total number of ADRs	0
Total number of ADRs of particular interest:	
Thrombotic microangiopathy	0
Thromboembolism	0
Arthralgia during emicizumab prophylaxis	0
Non-replacement treatment satisfation of the patient/caregiver n (%)	10 (100)

N - total number of patients; n - number of patients; Q2W - every 2 weeks; Q4W - every 4 weeks; ADRs - adverse drug reactions

DISCUSSION

Based on the levels of antihemophilic factor in the blood, hemophilia A is subdivided into mild (6-40% of normal FVIII activity), moderate (1 - 5% of normal FVIII activity), and severe hemophilia A (< 1% of normal FVIII activity) (4).

However, the bleeding phenotype of hemophilia A does not always correlate with the levels of FVIII activity in plasma, hence even some patients with mild hemophilia may have a severe bleeding tendency (5).

Regular prophylactic treatment in hemophilia A refers to the administration of either factor replacement agents or non-factor replacement agents in order to prevent bleeding, thus striving to achieve equality in terms of activities and quality of life between affected individuals and individuals without hemophilia (6).

Hemophilia A patients with a severe bleeding phenotype (including some patients with moderate hemophilia A who have a severe bleeding phenotype) require long-term prophylactic treatment, aiming to convert the severe bleeding phenotype into a moderate one, thus reducing the risk of both bleeding events, and the development/worsening of hemophilia complications (3 - 6). However, with the introduction of non-factor replacement agents, the goal of prophylaxis became even more ambitious - to reduce the number of bleeding events to zero (6).

In most affected patients, prophylactic therapy is being conducted via FVIII replacement (3, 4, 6).

Essentially, there are three main issues regarding FVIII replacement therapy.

Firstly, upon the intravenous administration of FVIII concentrate, the exogenous antihemophilic factor reaches its peak concentration in blood, which is followed by the gradual decline of its plasma concentration once the peak was reached (7). A trough is the minimal FVIII concentration required to maintain hemostasis, which was defined as a baseline level of FVIII activity of 1% (5). Once the FVIII plasma concentration drops below the trough level (FVIII activity < 1%), the risk of breakthrough bleeding increases, whereas the risk of joint bleeding increases much earlier, once the FVIII plasma activity has dropped below 15% (suggested as a "new trough") (5, 8). Optimal prophylaxis requires main-

taining the plasma concentrations of FVIII constantly above the trough level, which is challenging to achieve with replacement agents, as they typically demonstrate a wide variation between peak and trough levels (3, 6, 7). In fact, in case of replacement prophylaxis, an individual approach is required in order to establish an individual optimal target trough level, which is determined by multiple factors (type of physical activity, number of breakthrough bleeding episodes, presence/worsening of hemophilic arthropathy, results of thromboelastography and standardized thrombin generation tests) (5, 7).

Another issue of replacement prophylaxis lies in the fact that it is a life-long therapy which requires frequent repetitive intravenous administration of FVIII concentrate, resulting in damaging the patients' veins in time, compromising the venous access, which would be required for intravenous drug administration in the future (3, 4). Even though the development of extended plasma half-life FVIII concentrates (which are also admistered intravenously) has reduced FVIII administration frequency, (thus postponing the inevitable damaging of the veins), the three major issues of replacement prophylaxis remained unsolved (3).

The final major issue regarding replacement prophylaxis is a consequence of the peptide nature and high molecular mass of FVIII causing it to trigger formation of alloreactive plasma cells, which secrete anti-FVIII antibodies (inhibitors) upon repetitive exposure to the FVIII concentrate in certain patients (2, 4, 9). If a critically high titer of inhibitors is formed, these alloantibodies via immune mechanisms inactivate and eliminate FVIII, thus reducing plasma activity of the administered FVIII below trough, making replacement therapy inefficient for as long as high inhibitor titers persist (1, 2, 4, 6, 9).

All of the aforementioned issues have been resolved with the introduction of non-factor replacement prophylaxis for hemophilia A (3). A revolutionary breaktrough was made with the development of a chimeric humanized bispecific monoclonal antibody (emicizumab) which enables the activation of the coagulation cascade regardless of the absence of FVIII (3, 4). Emicizumab has two antigen binding sites of different specificity, one being specific for the activated ninth coagulation factor (FIXa), and the other being specific for the inactivated factor ten (FX) (3, 4, 10). Once emicizumab binds to both FIXa and FX, FIXa cleaves FX, causing its activation, which enables successful coagulation (4, 10). Emicizumab is a subcutaneous preparation used for non-factor replacement prophylaxis of severe phenotype hemophilia A regardless of the presence of inhibitors, while avoiding the peaks and troughs associated with replacement prophylaxis (3, 6).

The main criterion for the initiation of non-factor replacement prophylaxis in most of our patients (9/10 patients) was the impairment of the venous access, which was preventing us from the continuation of the former factor replacement prophylaxis, whereas in case of one adult patient the development of inhibitors was a dominant criterion for the initiation of non-factor replacement prophylaxis.

Annualized bleeding rate - ABR ("the number of total bleeding events divided by the number of months in the reporting time window and multiplied by 12") is a parameter used for the assessment of prophylactic treatment efficacy in hemophilia patients (3, 11). The goal ABR in the setting of non-factor replacement prophylaxis is considered to be ABR < 1.0 (12). This goal was achieved in case of our patients (median ABR = 0.0), since none had any bleeding events (including breakthrough bleeding) during the non-factor prophylactic treatment period. This therapeutic result may be attributed to the fact that emicizumab provides a consistent hemostatic capacity equivalent to the 20% residual level of FVIII activity (12).

There was no clear clinical deterioration of hemophilic arthropathy in the four patients with prior arthropathy during the period of non-factor prophylaxis. None of the patients without prior hemophilic arthropathy (6/10 patients) developed arthropathy during the period of non-factor prophylaxis. We were aware that joint status alone is not a reliable parameter for assessing non-factor replacement efficacy, and therefore we insisted on acquiring anamnestic data regarding arthralgia in our patients. None of our patients reported episodes of arthralgia during the period of non-factor prohylaxis.

Since even the bleeding of minimal duration (often subclinical, sometimes causing arthralgia) may cause long-term joint damage, early diagnosis and pediatric treatment is essential for the prevention of hemophilic arthropathy (6, 12). In cases of developed hemophilic arthropathy, patients would benefit from preventing further joint damage and preserving mobility as much as possible (5, 6). Unfortunately, there is hardly any long-term data on

either structure or function of affected joints in patients treated with emicizumab, thus the reported anamnestic data acquired from our patients should be interpreted with caution, permitting mild scepsis (3, 12). However, bearing in mind that the hemostatic capacity of emicizumab is similar to the 20% level activity of FVIII (based on chromogenic assays), and the fact that maintaining trough levels above 15% during the course of FVIII replacement prophylaxis lowers the risk of joint bleeding episodes, it would be reasonable to assume that emicizumab prophylaxis may prevent further deterioration of already existent hemophilic arthropathy and also prevent the onset of hemarthrosis in hemophilia A patients, though further studies are needed for the actual confirmation of this assumption (5, 12).

Besides injection site reactions, headache and arthralgia, potential adverse drug reactions (ADRs) of emicizumab may also include rare severe ADRs such as thrombotic microangiopathy and thromboembolism, as well as the loss of treatment efficacy due to the formation of anti-emicizumab antibodies (3, 10, 13). However, no ADRs occurred in our patients during the period of non-factor prophylaxis.

When interviewed regarding their satisfaction with the non-factor replacement prophylaxis compared to the prior factor replacement prophylaxis, all of our patients/caregivers reported greater satisfaction with the non-factor replacement prophylaxis.

We may attribute such a response to several factors (absence of bleeding events; median ABR = 0.0; subcutaneous route of administration; absence of joint disease deterioration; absence of ADRs during the period of non-factor prophylaxis), all associated with non-factor treatment safety, efficacy and commodity, which combined ensure the possibility of active engagement in physical, professional, and social activities, with improvement of serenity and self-esteem, thus providing our patients with the optimal quality of life (6).

Despite obvious limitations of this analysis, being conducted on a small number of patients within a short time interval, it represents the first step of our experience regarding non-factor prophylactic therapy in the University Clinical Center Niš.

The Republic Fund Of Health Insurance (Belgrade, Republic of Serbia) managed to provide the only licensed non-factor therapeutic alternative for a group of patients who were no longer fit for factor replacement prophylaxis, thus enabling them to have the best possible standard of care (6).

CONCLUSION

By providing safety from bleeding events and potentially the stability of affected joints, emicizumab prophylaxis enables greater activity and increases the quality of life of treated patients.

Our treatment results so far have been encouraging, but we must bear in mind that hemophilia A prophylaxis in patients with a severe bleeding phenotype is a life-long journey, and we should expect new challenges along the way.

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Mimetik antihemofiličnog faktora: novo poglavlje u profilaktičkom lečenju hemofilije A

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SAŽETAK

Uvod/Cilj. Hemofilija A je deficijencija antihemofiličnog faktora koja zahteva doživotno lečenje. Analizirali smo efekte profilaktičkog lečenja mimetikom antihemofiličnog faktora kod deset pacijenata muškog pola sa hemofilijom A.

Pacijenti i metode. Retrospektivna analiza sprovedena je na osnovu podataka o lečenju deset pacijenata muškog pola (četiri dečaka, jednog adolescenta i petorice odraslih) sa teškom hemofilijom A, koji su pre profilaktičkog lečenja emicizumabom profilaktički lečeni koncentratom antihemofiličnog faktora. Jedan odrasli pacijent razvio je inhibitore tokom profilakse antihemofiličnim faktorom. Kod četvorice odraslih pacijenata hemofilična artropatija razvila se pre početka profilaktičkog lečenja mimetikom antihemofiličnog faktora. Kod dvojice odraslih pacijenata profilaktičko lečenje emicizumabom sprovodilo se na četiri nedelje, a kod ostalih na dve nedelje. Nakon 14 meseci (u proseku) profilaktičkog lečenja mimetikom antihemofiličnog faktora analizirali smo broj probojnih krvarenja, godišnju stopu krvarenja, stanje zglobova, neželjene reakcije na emicizumab, kao i stepen zadovoljstva pacijenata lečenjem.

Rezultati. U toku profilakse emicizumabom nije bilo probojnih krvarenja. Nije došlo ni do kliničkog pogoršanja prethodno razvijene hemofilične artropatije kod pacijenata sa artropatijom. Vrednost godišnje stope krvarenja bila je jednaka nuli kod svih obolelih koji su lečeni emicizumabom. Kod naših pacijenata se u toku profilakse emicizumabom nisu javile neželjene reakcije na lek. Svi pacijenti istakli su da su zadovoljniji nesupstitucionim profilaktičkim lečenjem nego supstitucionom profilaksom.

Zaključak. Pružanjem zaštite od probojnih krvarenja i potencijalnim sprečavanjem daljeg oštećenja zahvaćenih zglobova, profilaktičko lečenje emicizumabom omogućava veću aktivnost i povećava kvalitet života lečenih pacijenata.

Ključne reči: **hemofilija, antihemofilični faktor, emicizumab, inhibitori, profilaksa**