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## EMICIZUMAB U TERAPIJI HEMOFILIJE A

### EMICIZUMAB IN THE TREATMENT OF HEMOPHILIA A

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#### Sažetak

**Uvod:** I pored značajnog napretka u terapiji Hemofilije A poslednjih decenija primenom koncentrovanih preparata osmog faktora, i dalje su povremeno prisutne epizode krvarenja. Pojava inhibitora značajno umanjuje efikasnost tradicionalne zamenske terapije, povećavajući značajno morbiditet i mortalitet kod ovih pacijenata. Emicizumab (HEMLIBRA<sup>®</sup>) je himerno bispecifično humanizovano antitelo koje premošćava aktivirani FIX i FX i tako ponovo uspostavlja funkciju aktiviranog FVIII koji nedostaje.

**Cilj:** Analiza literaturnih podataka o delovanju Emicizumaba u terapiji Hemofilije A.

**Rezultati:** Do sada sprovedene multicentrične randomizovane studije pod nazivom HAVEN su pokazale odlične rezultate ovog leka u lečenju pacijenata sa Hemofilijom A. Inhibitori FVIII se ne vezuju niti neutrališu emicizumab, pa samim tim nemaju uticaj na hemostatičku aktivnost leka. Profilaksa emicizumabom je dala značajnu redukciju lečenih krvarenja od 79% naspram grupe pacijenata na profilaksi bypassing agensima, a nakon dužeg praćenja čak 95%. I ostale studije su potvrdile dobre rezultate u lečenju i siguran bezbednosni profil, kako kod odraslih, tako i kod dece. U slučaju pojave krvarećih događaja ili pripreme za neodložnu hiruršku intervenciju, preporuka je davanje rFVII (NovoSeven)<sup>®</sup> po dosadašnjim vodičima.

**Zaključak:** Dosadašnji rezultati profilaktičke primene Emicizumaba pokazuju da se možda radi o revolucionarnom preparatu koji može značajno redukovati epizode krvarenja i popraviti kvalitet života pacijenata sa Hemofilijom A. Ipak, potrebno je dalje ispitivanje ovog leka.

**Ključne reči:** Emicizumab, hemofilija A, terapija

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#### Abstract

**Introduction:** Despite substantial advances in the treatment of Hemophilia A with the use of concentrated factor VIII preparations during recent decades, bleeding episodes still occur from time to time. The development of inhibitors significantly reduces the efficacy of traditional replacement therapy, seriously increasing morbidity and mortality in these patients. Emicizumab (HEMLIBRA<sup>®</sup>) is a chimeric bispecific humanized antibody that bridges activated FIX and FX and thus restores the function of missing activated FVIII.

**Aim:** The aim of the study was to analyze the literature data of the effect of Emicizumab in the treatment of Hemophilia A.

**Results:** Multicenter randomized studies called HAVEN have shown excellent results of this medication in the treatment of patients with Hemophilia A. FVIII inhibitors do not bind to or neutralize Emicizumab and therefore have no effect on the hemostatic activity of the drug. Emicizumab prophylaxis produced a significant reduction in treated bleedings of 79%, compared to with the group of patients on prophylaxis with bypassing agents, while the rate grew up to even 95% after longer observation. Other studies have also confirmed good treatment results and a favorable safety profile in both adults and children. In the cases of bleeding events or preparation for immediate surgical interventions, it is recommended to use FVII (NovoSeven)<sup>®</sup> according to previous guidelines.

**Conclusion:** The results of the prophylactic use of Emicizumab have so far shown that it may be a revolutionary preparation that can significantly reduce bleeding episodes and improve the quality of life of patients with Hemophilia A. Nevertheless, further testing of this drug is required.

**Key words:** Emicizumab, hemophilia A, treatment

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## Uvod

Nedostatak faktora VIII i sklonost ka krvarenju osnovne su karakteristike hemofilije A. Do pojave ove nasledne bolesti dolazi usled mutacije gena za VIII faktor, lociranog na dugom kraku X hromozoma. I pored značajnog napretka u terapiji hemofilije A, poslednjih decenija primenom koncentrovanih preparata osmog faktora, i dalje su povremeno prisutne epizode krvarenja. Naročito je izraženo kod pacijenata koji se leče po potrebi, a manje kod pacijenata na profilaktičkoj terapiji preparatima koncentrovanog VIII faktora. Pojava rekombinantnog preparata faktora VIII unapredila je efikasnost terapije i smanjila rizik od transmisionih bolesti. Takođe, pojava rekombinantnog preparata faktora VIII je, u razvijenim zemljama u poslednjih 25 godina, omogućila produženje prosečnog životnog veka do nivoa opšte muške populacije<sup>1</sup>.

Pojava anti-FVIII aloantitela predstavlja najznačajniju komplikaciju terapije i javlja se kod trećine obolelih sa teškom formom bolesti. Pojava inhibitora značajno umanjuje efikasnost tradicionalne zamenske terapije, povećavajući značajno morbiditet i mortalitet kod ovih pacijenata<sup>2</sup>. Dosadašnja terapija krvarećih epizoda kod pacijenata sa inhibitorima podrazumevala je primenu preparata premošćavanja (*bypassing agents*), kao što su koncentrat aktiviranog protrombinskog kompleksa (FEIBA)<sup>®</sup> i rekombinantnog aktivisanog faktora VII (NovoSeven)<sup>®</sup>.

Zbog toga se ukazala potreba za razvojem novih i efikasnijih hemostatskih preparata<sup>3</sup>.

### ***Emicizumab – novi terapijski pristup u lečenju hemofilije a***

Emicizumab (HEMLIBRA)<sup>®</sup> je himerno bispecifično humanizovano antitelo, koje premošćava aktivirani FIX i FX i tako ponovo uspostavlja funkciju aktiviranog FVIII, koji nedostaje, a neophodan je kako bi hemostaza bila delotvorna. Fiziološki mehanizam delovanja FVIII, po tipu prekidača uključeno isključeno, dejstvom emicizumaba preveden je u konstantni uključeni položaj<sup>4</sup>. Inhibitori FVIII ne vezuju se za emicizumab, niti neutrališu delovanje ovog antitela, pa samim tim nemaju uticaj na hemostatičku aktivnost leka.

## Introduction

Factor VIII deficiency and bleeding tendency are the basic characteristics of Hemophilia A. The appearance of this inherited disease is due to a mutation in the factor VIII gene located on the long arm of the X chromosome. Despite substantial advances in the treatment of Hemophilia A with the use of concentrated factor VIII preparations during recent decades, bleeding episodes still occur occasionally. It is especially pronounced in patients who are treated on-demand, and less so in patients on prophylactic therapy with concentrated factor VIII preparations. The appearance of a recombinant factor VIII preparation has improved the efficacy of treatment and reduced the risk of communicable diseases. In the last 25 years in developed countries, it has also enabled the extension of the average life expectancy to the level of a general male population<sup>1</sup>.

The appearance of anti-FVIII alloantibodies is the most significant treatment complication and occurs in one third of patients with a severe form of the disease. The development of inhibitors significantly reduces the efficacy of traditional replacement therapy, seriously increasing morbidity and mortality in these patients<sup>2</sup>. Previous treatment of bleeding episodes in patients with inhibitors has involved the use of bypassing agents such as activated prothrombin complex concentrate (FEIBA) and recombinant activated factor VII (NovoSeven)<sup>®</sup>.

Therefore, the need has been felt for the development of new and more efficient hemostatic preparations<sup>3</sup>.

### ***Emicizumab – a new therapeutic approach in the treatment of hemophilia a***

Emicizumab (HEMLIBRA)<sup>®</sup> is a chimeric bispecific humanized antibody that bridges activated FIX and FX and thus restores the function of missing activated FVIII, and it is essential for hemostasis to be effective. The physiological “on-off” switch mechanism of FVIII performance was converted into a constant “on” position by the action of Emicizumab<sup>4</sup>. FVIII inhibitors do not bind to or neutralize Emicizumab and therefore have no effect on the hemostatic activity of the drug.

So far, multicenter randomized studies called HAVEN have shown excellent results of this medicine in the treatment of patients with Hemophilia A.

### **Rezultati primene emicizumaba**

Do sada sprovedene multicentrične randomizovane studije pod nazivom *HAVEN* pokazale su odlične rezultate ovog leka u lečenju pacijenata sa hemofilijom A.

*HAVEN* 1 studija objavljena 2017. godine uključivala je 109 pacijenata starijih od 12 godina sa visokim titrom inhibitora. Godišnja stopa krvarenja (ABR) iznosila je 2,9 događaja u grupi pacijenata na profilaksi emicizumabom, naspram 23,3 ABR u grupi pacijenata bez profilakse, što predstavlja razliku od 87% u korist profilakse emicizumabom. Profilaksa emicizumabom dala je značajnu redukciju lečenih krvarenja od 79%, naspram grupe pacijenata na profilaksi bypassing agensima, a nakon dužeg praćenja redukciju od čak 95%. Ozbiljni neželjeni događaji zabeleženi su kod 3 pacijenta u vidu trombotične miroangiopatije i kod 2 pacijenta sa trombotičnim događajima, ali samo kada je aPCC (FEIBA)<sup>®</sup> uporedo primenjivana u prosečnoj dozi većoj od 100 U/kg dnevno<sup>5</sup>.

*HAVEN* 3 studija uključila je 152 pacijenta starija od 12 godina bez prisustva inhibitora. Značajna redukcija lečenih krvarenja od 97% postignuta je u grupi pacijenata lečenih emicizumabom, naspram grupe pacijenata lečenih na zahtev preparatima koncentrovanog FVIII. Takođe, zabeležena je značajna redukcija lečenih krvarenja od 68% je iznosila u odnosu na grupu pacijenata na profilaksi koncentrovanim FVIII. Nije bilo ozbiljnijih neželjenih događaja.

I ostale studije su potvrdile dobre rezultate u lečenju i siguran bezbednosni profil, kako kod odraslih, tako i kod dece<sup>6</sup>.

Doziranje leka je u prve 4 nedelje 3 mg/kg (udarna doza), a zatim se nastavlja dozom održavanja od 1,5 mg/kg nedeljno ili 3 mg/kg jednom u 2 nedelje ili 6 mg/kg jednom u 4 nedelje.

Lek je registrovan u više od 90 zemalja. U Srbiji je registrovan za profilaktičko lečenje pacijenata sa hemofilijom A, ali je na pozitivnoj listi samo za pacijente sa prisustvom inhibitora.

U slučaju pojave krvarećih događaja ili pripreme za neodložnu hiruršku intervenciju, preporuka je davanje rFVII (NovoSeven)<sup>®</sup>, po dosadašnjim vodičima.

Uticaj leka emicizumab na testove, koji se rutinski primenjuju u hemofiliji, poseban je problem<sup>7</sup>. Emicizumab značajno utiče na rezultate sledećih testova: aktivisano parcijalno tromboplastinsko vreme (aPTT), aktivnost FVIII i titar inhibitora FVIII.

### **Rezults of therapeutic approach with emicizumab**

The *HAVEN* 1 study published in 2017 included 109 patients older than 12 years with high-titer inhibitors. The annualized bleeding rate (ABR) was 2.9 bleedings in the Emicizumab prophylaxis group, compared with 23.3 ABR in the prophylaxis-free group, which represents a difference of 87% in favor of Emicizumab prophylaxis. Emicizumab prophylaxis produced a significant reduction in treated bleedings of 79%, compared to the group of patients on prophylaxis with bypassing agents, while the rate grew up to even 95% after longer observation. Serious adverse events were reported in 3 patients in the form of thrombotic myoangiopathy and in 2 patients with thrombotic events, but only when aPCC (FEIBA)<sup>®</sup> was co-administered at an average dose higher than 100 U / kg per day<sup>5</sup>.

The *HAVEN* 3 study included 152 patients 12 years of age or older without the presence of inhibitors. A significant reduction of 97% in treated bleedings was achieved in the emicizumab-treated group versus the group treated on-demand with concentrated FVIII preparations. Also, a significant reduction in treated bleedings of 68% was recorded in relation to the group on prophylactic therapy with concentrated FVIII. There were no serious adverse events.

Other studies have also confirmed good treatment results and a favorable safety profile in both adults and children<sup>6</sup>.

The dosage of the medicament is 3 mg/kg (loading dose) in the first 4 weeks, and then it is continued with a maintenance dose of 1.5 mg/kg per week or 3 mg/kg once in 2 weeks or 6 mg/kg once in 4 weeks.

The drug is registered in more than 90 countries. In Serbia, it is registered for the prophylactic treatment of patients with Hemophilia A, but it is in the positive list of medications only for patients with the presence of inhibitors.

In the cases of bleeding events or preparation for unpostponable surgical intervention, it is recommended to use rFVII (NovoSeven)<sup>®</sup> according to previous guidelines.

The effect of Emicizumab on tests routinely applied in hemophilia represents a particular problem<sup>7</sup>. Emicizumab significantly affects the results of the following tests: activated partial thromboplastin time (aPTT), FVIII activity and FVIII inhibitor titers. In order to get the correct results, it is necessary

Da bi se dobili ispravni rezultati, potrebno je raditi hromogene testove, ali je malo laboratorija opremljeno ovim testovima. Radi se na rešenju ovog problema.

Inače, kod pacijenata koji primaju emicizumab profilaktički, nema potrebe za testiranjem u vezi primene leka.

### **Zaključak**

Dosadašnji rezultati profilaktičke primene emicizumaba pokazuju da se možda radi o revolucionarnom preparatu, koji može značajno redukovati epizode krvarenja i popraviti kvalitet života pacijenata sa hemofilijom A. Ipak, potrebno je dalje ispitivanje ovog leka, u smislu njegove efikasnosti i bezbednosti, kao i primene sa drugim lekovima u posebnim situacijama (krvareće epizode, priprema za hirurške intervencije).

to do chromogenic tests, but few laboratories are equipped with these tests. Efforts are being made toward solving this problem.

Apart from that, in patients receiving prophylaxis with Emicizumab, there is no need for testing regarding the use of medication.

### **Conclusion**

Previous results of the prophylactic use of Emicizumab have so far shown that it may be a revolutionary preparation that can significantly reduce bleeding episodes and improve the quality of life of patients with Hemophilia A. However, further testing of this drug is needed, in terms of its efficacy and safety, as well as its co-administration with other drugs in special situations (bleeding episodes, preparation for surgical interventions).

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