

New Treatment Modalities in Hemophilia

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ABSTRACT

Hemophilia is a single gene disorder and as a genetical coagulation system problem it is a life-long bleeding disorder. Even though routine treatment modalities as plasma-derived and then recombinant factor concentrates available for last 50 years, unmet needs is continuing for hemophilia therapy. Gold standart treatment is regularly prophylactic FVIII/ FIX infusions. However, life-long and frequent intra-venous infusions become medical burden for patients and families. New agents as enhanced half-life (EHL) factor concentrates and non-factor therapies which are able to be used subcutaneously are very hopeful. In this review, EHL factor concentrates, FVIII mimetic agents and re-balancing therapies will be discussed. Although cellular gene therapy is very hopeful and successful phase-3 studies are reported, gene therapy for hemophilia will not be mentioned in this review.

Keywords: Hemophilia, FVIII, FIX, EHL-products, emicizumab, fitusuran, concizumab

INTRODUCTION

Hemophilia-A is one of the rare hematological and genetical diseases. Prevalance rate is 1/10.000 and incidence is 1/5000 in male neonates. Hemophilia-B is also seen with a prevalence rate of 1/50.000. Both disorders are X-linked, recessive and genetically transmitted disorders.¹⁻³ Even though hemophilia is a rare disorder; factor concentrates which are used in the treatment for many years are not orphan drugs. Because, in Western countries, approximately for 50 years, firstly plasma-derived FVIII and F-IX products and then the recombinant factor concentrates for the last 20 years have been widely used in routine practice. Gold standard of hemophilia therapy is prophylaxis.¹⁻³

As Turkish hematologists and as Turkish patients with hemophilia as well; we are lucky that Turkey is one of the ten nations in the world where factor concentrates for prophylaxis of hemophilia patients are re-imbursed. Really, most of the severe hemophilia patients are in prophylaxis regimen. Hemophiliac arthropathies are being significantly decreased for last 10 years thanks to prophylaxis.⁴

However, burden of disease is so heavy for hemophilia patients and families. Unmet needs are continuing. First of all, hemophilia is a life-long disorder. Prophylaxis must be given via intravenous route for a long-time. Venous access is a common problem for patients. Especially, during adolescent period, adherence problems to IV infusions are very well-known.^{2,3}

All new therapeutic modalities will be discussed at the following.

Gene therapy is another treatment way for hemophilia due to the fact that hemophilia-A and hemophilia-B are single gene disorders. Phase-3 clinical studies are continuing nowadays. According to authorities, Food and Drug Administration (FDA) and European Medicines Agency (EMA) will give approval for HA and HB in 2022. Gene therapy is excluded from this review and will be discussed in another time.^{5,6}

FVIII and FIX Products with Enhanced-half Life

Due to relatively short half-life of regular factor concentrates, frequent intravenous infusions are needed to maintain plasma FVIII levels. Technologies used for enhanced half-life (EHL)

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products are PEGylation, fusion protein technology (Fc part of immunoglobulin and albumin) and single-chain technology.^{7,8}

In respect of new modalities, firstly enhanced-FVIII and IX products came into routine practice. For the last 5 years EHL-FVIII products were used for real-life conditions. These products were preferred for less frequent FVIII infusions and greater FVIII levels. However EHL-FVIII products did not bring definitive solution due to relatively low elevation (1.5 fold) in half-life. Some adult hemophilia-A patients are able to use once weekly programs. For children, twice weekly FVIII infusions are seen in the real-life conditions. Whereas, for hemophilia-B, EHL-FIX products are being used in every 7-10 days due to 4-5 fold increased half-life. In Western countries, EHL-FVIII and EHL-FIX products are now used for most of the patients in prophylactic regimens. In Turkey, some EHL-FVIII products received approval from the Ministry of Health, however re-imburement agency (SGK) did not yet accept re-imburement. Now, in Turkish market, all plasma-derived products and all regular recombinant FVIII/FIX products are available in re-imburement list.⁴

The reason why for limited enhanced-FVIII half-life (maximum 1.5 fold) with the PEGylation and Fusion technologies is dependent on the half-life of von Willebrand factor. However, Sanofi has developed another technology called as "BVV-001 X-TEN Technology" which is not dependent on vWF half-life. With this technology following IV prophylaxis every 10 days, FVIII level is maintained more than 10% for the next 10 days. So, more than 10% FVIII level will provide better prevention against hemophilic arthropaties in future. This regimens used with real FVIII products seem futural therapy for hemophilia-A (Table 1).⁹

Non-factor Therapies in Hemophilia

1. FVIII mimetic agents (Bi-specific antibodies),
2. Re-balancing therapies: Inhibitory monoclonal antibodies to natural anti-coagulant proteins in the blood stream as tissue factor pathway inhibitor (TFPI), antithrombin and/or protein-C.

Bispecific Antibodies for Hemophilia (FVIII Mimetic Agents)

Genetic defect in hemophilia-A is a mutation in the FVIII gene. In a patient with hemophilia-A, FVIII protein synthesis is not functional and not effective for hemostasis. In normal physiological conditions, For FXa, F-IX and FVIII should be available. In hemophilia-A patients, FVIII protein is not normal. In this new treatment regimen, bispecific antibodies are available. Both Fab arms of monoclonal antibody bind F-IXa and FX. The result of biological reaction is the development of FXa. So, new agent mimics of FVIII effect in coagulation process. Thrombin accumulation is final outcome for hemotasis.^{10,11}

Emicizumab (Roche)

Emicizumab, a spesific monoclonal antibody that bridges FIXa and FX to allow the coagulation process to continue as a physiological hemostasis reaction. Emicizumab has been a life-transforming therapy for patients with or without inhibitors. This molecule is so important in history of hemophilia therapies. It is the first approved subcutaneous (SC) agent for hemophilia-A. Emicizumab was firstly licenced by FDA and EMA for patients with hemophilia-A with inhibitors.^{10,11} Then it was approved in patients without inhibitors for HA. HAVEN studies were successfully completed before approvals.¹²⁻¹⁵

Table 1. Approved enhanced FVIII and F-IX products in Western countries

Generic name	Brand name and company	Technic for enhancing half-life	Practical using in Western countries
Efral-octocog	ELOCTATE/ELOCTA (Sanofi/Sobi)	Fusion protein (FVIII/Ig) Half-life: 19 h.	Approved 5 years ago by FDA and EMA. Not yet for Turkey as March, 2022
Damactocog	JIVI (Bayer)	PEGylated FVIII (60 kDa) Half-life: 19 h.	FDA approved two years ago. Turkish MoH approved in 2021 September
Octococ pegol	ADYNOVATE (Takeda)	PEGylated FVIII (2x20 kDa) Half-life: 14.3 h.	FDA approved 3 years ago.
Turoctocog pegol	ESPEROCT (Novo Nordisk)	PEGylated FVIII (40 kDa) Half-life: 19 h.	FDA approved last year.
rFIX-Fc	ALPROLIX (Sanofi/Sobi)	Fusion protein (F-IX/Ig) Half-life: 82 h.	It was approved 6 years ago. There is real-life experience in US and Europe. It is possible to use every 7 days
rF-IX- FP	IDELVION (CSL-Behring)	Fusion propein (F-IX/albumin) Half-life: 102 h.	Possible to use every 10 days for prophylaxis
Nonacoc pegol	REFIXIA (Novo Nordisk)	PEGylated protein F-IX Half-life: 96 h.	Possible to use every 7-10 days for prophylaxis
Efanés-octococ	BIVV-000-1 (Sanofi) rFVIIIc-vWF-X-TEN	X-TEN technology for EHL-FVIII	Not yet approved , phase-3 trial was completed. Possible to use every 10 days

FDA: Food and Drug Administration, EMA: European Medicines Agency

The HAVEN-1 study¹² was performed on adult patients with inhibitors. The first thrombotic events were observed in this study. Three patients with thrombo-microangiopathy and two patients with thrombo-embolism were reported. Mechanism of thrombotic events was evaluated as the combination of aPCC (FEIBA) and emicizumab. Today in the real-life conditions, combination with Emicizumab and aPCC is medically forbidden.^{10,13} HAVEN-2 study¹³ was performed for children with hemophilia-A with inhibitors. We also joined this internationally study with 8 Turkish patients from three expert centers including İzmir, İstanbul and Adana. We showed that Emicizumab was safe and effective for children with inhibitors. The MoH approved this molecule for every indications in HA in September 2019. However SGK has not yet approved it for re-imburement. By the way, emicizumab (Hemlibra/Roche) has reached more than 10.000 hemophilia-A patients in Western countries.

Hemlibra is weekly loaded at a dose as 3 mg per kg SC. Then for weekly application, maintenance dose is 1.5 mg/kg. If you would like to use every two weeks, dose will be 3 mg/kg or for monthly dose the dose is 6 mg/kg.^{14,15} The recommendation for children is SC injection every two weeks due to much less volume. Laboratory monitoring is not needed in routine practice. For breakthrough bleeds in non-inhibitory patients, FVIII treatment should be administered at a normal dose. Breakthrough bleeds in patients with inhibitors are so different. First preferred by-pass agent must be rFVIIa (Novo Seven). Avoiding the use of aPCC (FEIBA) is important point and if required, lowest dose (50 IU/kg) of aPCC should be used.¹⁰

In hemophilia-B, unfortunately emicizumab is not effective. Because for it's effectivity, F-IX and F-X must be functionally available. Due to functional problem in F-IX in hemophilia-B, Hemlibra is ineffective (Table 2).¹⁰

Mim-8 (Novo Nordisk)

Mim-8 is another bispecific monoclonal antibody. However, it is not yet approved and phase-3 clinical study for adults has been initiated on 2022. We also studied with this agent in phase-2 study with success. The mechanism of action is similar to emicizumab. The molecule is given subcutaneously. However, only weekly and monthly SC options are available.¹⁶

Definition of "next-generation" FVIII mimetics fits with Mim-8. Because Mim-8 is highly potent molecule bridging FIXa and FX in

development for SC therapy. Mim-8 optimization process is aimed for efficient activation of FX by FIX in the presence of procoagulant membrane (as phospholipid membrane), minimal target binding, and low immunogenicity risk. Mim-8 also has a high potency allowing for administration of small volume in a pen device.¹⁶

Re-Balancing Therapies

These type of therapies are interestingly effective in balancing coagulant/anticoagulant proteins. Another interesting point is FVIII or F-IX activities stay <1% during these treatments. Elevated thrombin levels are so important for gaining balance. The main characteristic of these therapeutic agents is inhibition of TFPI, antithrombin and protein-C. The most important point is efficacy in either HA or HB patients. So, patients with HB will be happy and hopeful with these agents. They were determined as official orphan drugs by FDA.³

Anti-TFPI Molecules

Concizumab (Novo Nordisk)

Mechanism of action is inhibitory effect to TFPI protein as a monoclonal antibody. This molecule is used daily with SC injections. However special insulin-like pens from Novo Nordisk are provided as an easy application. As a clinical center, we were in the phase-1^{17,18} and phase-2 studies¹⁹ and last year we initiated phase-3 study with success. Not only HA but also HB patients are nominates for this monoclonal antibody. FDA gave an orphan drug competence for HB patients with inhibitors.

Marstacimab (Pfizer)

This molecule can be used weekly or two weekly as SC infusions in HA and HB patients. Turkey is also one of the countries recruiting most patients for phase-3 study and it is continuing.²⁰

Antithrombin Agents

Fitusuran (Sanofi)

Fitusuran is designed to lower antithrombin, a protein that inhibits blood coagulation, with the goal of promoting sufficient thrombin generation to re-balance hemostasis and prevent new bleeds. RNA-interference is a unique therapy for HA and HB patients with and without inhibitors. Interestingly, this molecule is used in every one month via SC route. Mechanism of action is antithrombin activity.

Table 2. Emicizumab and physiological FVIII comparison in coagulation balance		
Comperative parameters	Physiological activated FVIII (FVIIIa)	Emicizumab (ACE910)
Interaction sites	Multiple sites of interaction	Single site of interaction
Affinity	High affinity for enzyme and substrate	Low affinity
Specificity	Specific for FIXa and FX (no binding to FIX and FXa)	FIX vs FIXa and FX vs FXa bindings possible
Co-factor activity	Full cofactor activity as phospholipid membrane binding/bridging from IX to Xa/FIXa stability	Partial cofactor activity only bridges FIXa to FX
On-off system	FVIIIa has a on-off system	EMI has no on-off system

However this effect reflects RNA inhibition in the hepatocyte level. Nowadays phase-3 studies are continuing.^{3,21,22}

We are inside the ATLAS studies with 12 patients with HA and HB. Our experience with fitusuran has reached to four years. Now, protocol was changed after some thrombotic events. We use SC injections every 2 months now. Patients and families are so happy with this therapeutic modality. Interestingly, Turkey, India and Korea are the most recruiting countries for ATLAS studies.

In 2021 ASH congress, data from phase-3 studies showed that fitusuran significantly reduced bleeds in patients with hemophilia-A and hemophilia-B, with or without inhibitors.^{21,22} Original portocol was 80 mg fitusuran SC in every month with control of alanine aminotransferase-aspartate aminotransferase levels. After protocol revision related with thrombo-embolic events in the study, dose was reduced to 50 mg in every two months. By the way, pediatric fitusuran phase-3 study was started in 2021, globally. Our center is one of the centers as always.

Anti-Protein C Agents

Serpin-PC (Apcintex/Centessa)

The last balancing molecule is Serpin-PC. Phase-1 and phase-2 studies³ showed that it was a safe and efficient molecule when used SC. In 2022, phase-2B clinical trials will be started in Western countries and probably in Turkey²³.

CONCLUSION

Factor products with EHL mostly replaced regular factor products in Western countries. Much less IV infusion and very high trough factor levels are two biggest advantages for these products. However, they are used intravenously. So, future of SC agents seems more brightful for hemophilia therapies. SC application and very less frequency of injections (as weekly or as monthly) are very important unmet needs for current hemophilia therapy. In Western countries, 90% of patients with inhibitors and 50% of patients without inhibitors with HA have proceed to emicizumab. Unfortunately there is no SC agent approved for HB patients. Of course in future, fitusuran and concizumab are very hopeful and important options. Gene therapy wih AAV-based technology is being investigated in phase-3 studies. Approval time of FDA and EMA may be 2022.

Ethics

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