Non-factor replacement therapy for haemophilia: a current update

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Abstract

One of the most challenging issues facing us in the treatment of haemophilia is the development of alloantibodies against infused factor VIII (FVIII) or factor IX (FIX). Inhibitors render factor replacement therapy ineffective, exposing patients to an unacceptably high risk of morbidity and mortality. Besides the well-known bypassing agents (i.e. activated prothrombin complex concentrate and recombinant activated factor VII) used to treat or prevent bleeding in haemophilia patients with inhibitors, there is growing interest in a new class of therapeutic agents which act by enhancing coagulation (i.e. emicizumab) or inhibiting anticoagulant pathways (i.e. fitusiran and concizumab). This review will focus on these innovative therapies, providing an update on their current stage of clinical development.

Keywords: haemostatic agents, ACE910, emicizumab, antithrombin, concizumab.

Introduction

The most challenging complication in the treatment of haemophilia is currently the development of anti-FVIII or -FIX alloantibodies, which affect approximately one-third of patients with severe haemophilia A and approximately 3-5% of those with severe haemophilia B[1-4]. Such inhibitors, that neutralise the functional activity of FVIII and FIX clotting factors administered with replacement therapy, impact patients access to a safe and effective care, and predispose them to an increased risk of morbidity and mortality[5]. Two therapeutic options can be considered for haemophilia patients with inhibitors: haemostatic therapy to prevent or treat bleeding episodes, and inhibitor eradication[5]. Regarding the former type of treatment, the introduction of agents that bypass the functional activity of FVIII and FIX, such as activated prothrombin complex concentrates (aPCC, Factor Eight Inhibitor Bypassing Activity - FEIBA, Baxalta) and recombinant activated factor VII (rFVIIa, NovoSeven, Novo Nordisk), has dramatically improved the management of acute bleeding in inhibitor patients, allowing home treatment and a substantial amelioration of their quality of life[6-8]. Recently, recombinant porcine FVIII has also been developed as a new haemostatic therapy, even though it is currently licensed only for acquired haemophilia A[9]. In fact, inhibitor eradication is currently mostly performed through immune tolerance induction (ITI) therapy, which is able to suppress alloantibodies in up to 70% of haemophilia A and 50% of haemophilia B patients with inhibitors[8]. In addition to this therapeutic scenario, alternative pharmacological therapies have recently been developed and are currently at an advanced stage of clinical investigation[8,10-13]. These agents are based on innovative technologies able to enhance the haemostatic potential independently of replacement factor administration. The most interesting of them acts by amplifying the coagulation cascade to generate thrombin (emicizumab) or by inhibiting naturally occurring anticoagulant pathways (fitusiran and concizumab) (Table I)[8]. This review will look at the main characteristics of these non-factor therapies and their current stage of development.

Search methods

We analysed the medical literature for published

Table I - Non-factor replacement therapy for haemophilia.

	Product		
	Emicizumab	***Fitusiran***	***Concizumab***
Manufacturer	Chugai Pharmaceutical/ Hoffman-La Roche	Alnylam Pharmaceuticals	Novo Nordisk
Technology	Chimeric bispecific humanised antibody	siRNA	Humanised monoclonal antibody
Mechanism of action	FVIIIa-mimetic	Antithrombin inhibition	TFPI inhibition
Dosing frequency	Weekly	Weekly to monthly	To be determined
Route of administration	SC	SC	SC
Stage of development	FDA approved	Phase II-III	Phase II

siRNA: short interfering RNA; TFPI: tissue factor pathway inhibitor; SC: subcutaneous; IV: intravenous; FDA: Food and Drug Administration.

studies on novel therapeutic approaches for haemophilia treatment. The MEDLINE electronic database was searched without temporal limits using the English language as a restriction. The Medical Subject Heading and key words used were: "newer haemostatic agents" AND "novel haemostatic agents" AND "investigational drugs" AND "alternative therapies" AND "haemophilia A" AND "haemophilia B" AND "inhibitors" AND "by-passing agents" AND "emicizumab" AND "ACE910" AND "antithrombotic pathway" AND "anticoagulant pathway" AND "tissue factor pathway inhibitor (TFPI)" AND "concizumab" AND "antithrombin" AND "RNA interference (RNAi)" AND "ALN-AT3" AND "fitusiran". We also screened the reference lists of the most relevant review articles for additional studies not captured in our initial literature search. Search terms were also applied to abstracts from the latest international congresses on haemostasis, thrombosis and haematology.

Emicizumab

Emicizumab (ACE910; Hoffman-La Roche and Chugai Pharmaceutical) is a chimeric bispecific humanised antibody directed against FIXa and FX, which mimics the co-factor function of FVIII. It binds to the enzyme FIXa with one arm and to the FX zymogen with the other, placing both in spatially appropriate positions and thereby promoting FIXa-catalysed FX activation and tenase formation[14-16]. However, despite this mechanism, it should be emphasised that FVIII and emicizumab differ profoundly from each other in terms of affinity, regulation, topology and FIXa-enhancing activity, as recently reviewed by Lenting and Colleagues[17].

In a short-term primate model of acquired haemophilia A, ACE910 given as single intravenous bolus of 1 or 3 mg/kg did control artificially-induced muscle or subcutaneous bleeds to the same degree as recombinant porcine FVIII infused at twice-daily intravenous doses of 10 U/kg[18]. In a long-term primate model of acquired haemophilia A, weekly subcutaneous doses of ACE910 (initially 4 mg/kg, followed by 1 mg/kg) prevented bleeding episodes, including joint bleeding[19], making this agent potentially attractive for prophylactic use in both inhibitor and non-inhibitor haemophilia patients. The first study in humans[20] was conducted in healthy male adults (40 Japanese and 24 Caucasian men) receiving a single subcutaneous injection of emicizumab up to 1 mg/kg bodyweight. Emicizumab showed a linear pharmacokinetic (PK) profile in these healthy volunteers and a half life of approximately 4-5 weeks. In *ex vivo* FVIII neutralised plasma of the participants, the bispecific antibody shortened activated partial thromboplastin time and increased the peak height of thrombin generation in a dose-dependent manner. No serious adverse events were recorded[20]. An open-label, non-randomised, dose-escalation phase I study enrolling 18 Japanese severe haemophilia A patients (11 with and 7 without inhibitors) receiving once-weekly subcutaneous administration of emicizumab at doses of 0.3, 1 or 3 mg/kg for 12 weeks was published in 2016 by Shima and Colleagues[21]. The end points were safety and PK profiles, as well as the annualised bleeding rate. The authors observed a marked reduction in the median annualised bleeding rates, which decreased from 32.5 to 4.4 (0.3 mg/kg group), 18.3 to 0.0 (1 mg/kg group), and 15.2 to 0.0 (3 mg/kg group), respectively. No bleeding was observed in 73% (8/11) of patients with FVIII inhibitors and in 71% (5/7) of patients without inhibitors. A long-term extension of this study documented the safety profile of emicizumab, with no thromboembolic events reported and no neutralising anti-emicizumab antiobodies developing during the course of the study[22]. Very recently, the phase III open-label, multicentre, randomised HAVEN 1 trial was published, enrolling a total of 109 subjects aged 12 years or older with haemophilia A and inhibitors[23]. The annualised bleeding rate was 2.9 events (95% confidence interval [CI]: 1.7-5.0) among participants randomly assigned to emicizumab prophylaxis *vs* 23.3 events (95% CI: 12.3-43.9) among those assigned to no prophylaxis, representing a significant difference of 87% in favour of emicizumab prophylaxis ($p<0.001$). In a first-ever intra-patient analysis, emicizumab prophylaxis resulted in a reduction in treated bleeds of 79% ($p<0.001$) compared to previous prophylaxis treatment with bypassing agent collected in the frame of a non-interventional study prior to enrollment[23]. Serious side effects including thrombotic microangiopathy in 3 cases and other thrombotic events in 2 cases were reported, which were associated with cumulative doses of aPCC >100 U/kg/24 hours administered for the treatment of breakthrough bleeds during emicizumab prophylaxis. No events were reported when emicizumab was given alone or in conjunction with rFVIIa[23]. A possible explanation of this increased thrombotic incidence lies in the fact that the activity of the bispecific antibody is predominantly dependent on the amount of FIXa that is generated (aPCC contains FIXa)[17]. To reduce the thrombotic risk, a recommendation for the use and dosing of bypassing agents (to avoid the use of aPCC, if possible, as well as to use the lowest doses of approved bypassing agents) during emicizumab prophylaxis was released by the manufacturer and no new adverse events were recorded in an updated analysis with a follow up that was nearly six months' longer[24].

Interim results from the pivotal HAVEN 2 phase III study, enrolling 20 children aged 2-12 years of age with haemophilia A and inhibitors, showed that 87% of patients who received once-weekly emicizumab prophylaxis

experienced no bleed[25]. In an intra-patient analysis of 13 children who had participated in the non-interventional study, emicizumab prophylaxis resulted in a 99% reduction in treated bleeds compared to previous treatment with a bypassing agent, either as prophylaxis or as on-demand therapy; the annualised bleeding rate for treated bleeds was 17.2 events (95% CI: 12.4-23.8) on previous treatment with a bypassing agent and 0.2 events on emicizumab prophylaxis[25]. These results were confirmed in an up-dated analysis including six additional months of follow up and 40 additional patients[26]. No serious adverse events were reported, including no thromboembolic or thrombotic microangiopathy episodes, nor were anti-drug antibodies observed.

Two additional phase III studies are currently ongoing: HAVEN 3 (NCT02847637), which is evaluating emicizumab prophylaxis dosed once weekly or once every other week in patients 12 years of age or older with haemophilia A without inhibitors, and HAVEN 4 (NCT03020160), which is evaluating emicizumab prophylaxis dosed every four weeks in people 12 years of age or older with haemophilia A with or without inhibitors. Recently, this agent has received the approval from the US Food and Drug Administration (FDA), under the name of Hemlibra, for haemophilia A patients with FVIII inhibitors.

Fitusiran

Another interesting therapeutic approach in haemophilia involves the inhibition of the main naturally-occurring anticoagulant antithrombin, which acts by inactivating FXa and thrombin. This approach was experimentally supported by results obtained in a mouse model of haemophilia A, showing that reduction of the plasma levels of antithrombin improved thrombin generation and was associated with a less severe bleeding phenotype[27]. Exploiting RNA interference (RNAi), i.e. the natural process of gene silencing that occurs in various organisms, including plants and mammalians, the short-interfering RNA (siRNA) ALN-AT3 (Fitusiran, Alnylam Pharmaceuticals) has been developed in order to suppress antithrombin synthesis in hepatocytes[28,29]. In a pre-clinical study in various animal models of haemophilia, subcutaneous administration of fitusiran showed potent, dose-dependent and durable reduction of antithrombin plasma levels, restoring haemostasis and improving thrombin generation[30]. A phase I dose-escalation study based upon the subcutaneous administration of ALN-AT3 in 4 healthy volunteers and 25 patients with severe or moderate haemophilia A or B without inhibitors was recently published[31]. The healthy participants received a single subcutaneous injection of fitusiran (0.03 mg/kg) or placebo. The haemophilia patients received three injections of fitusiran either once weekly (0.015, 0.045, or 0.075 mg/kg) or once monthly (0.225, 0.45, 0.9, or 1.8 mg/kg, or at a fixed dose of 80 mg)[31]. The single fitusiran dose and the weekly treatment regimens both produced consistent and sustained drops in plasma antithrombin levels, which supported the adoption of a longer interval between doses. The monthly regimen, indeed, induced a dose-dependent mean maximum reduction of antithrombin of 70-89% from baseline. Notably, the decreases in antithrombin levels varied little during the weeks between doses and were associated with increased thrombin generation, regardless of whether patients had haemophilia A or B[31]. No thromboembolic episodes were recorded during the study period. Thus, based on these results, and in order to assess its long-term safety and efficacy, the investigators selected once-monthly, fixed doses of fitusiran 50 and 80 mg for the phase II open-label extension (OLE) study, which included 33 patients (14 with inhibitors and 19 without inhibitors). Interim results from the OLE study were recently presented[32]. At a median of 13 months after the first fitusiran dose, patients at both dose levels experienced a nearly 80% reduction in antithrombin levels. Exploratory post-hoc analysis of bleeding events showed a median annualised bleeding rate of 1 event in patients without inhibitors and 0 in those with inhibitors. All intercurrent bleeding events were successfully managed with replacement factor (patients without inhibitors) or bypassing agent (patients with inhibitors). No thromboembolic episodes were recorded. A phase III clinical programme (ATLAS) evaluating fitusiran 80 mg once-monthly is under way. The programme is designed to evaluate the safety and efficacy of fitusiran in three separate trials, including patients with haemophilia A and B with (ATLAS-INH) or without (ATLAS-A/B) inhibitors, and patients receiving prophylactic therapy (ATLAS-PPX). However, in September 2017, a serious thromboembolic event (sinus vein thrombosis) with fitusiran was reported in a patient without inhibitors (enrolled in the OLE study) who had concomitantly received three doses of FVIII[33]. Following this adverse event, the manufacturer immediately suspended all ongoing trials on fitusiran. In November 2017, the manufacturer announced it had achieved an alignment with the FDA on new clinical risk mitigation measures, including protocol-specified guidelines and additional investigator and patient education concerning reduced doses of replacement factor or bypassing agent to treat any breakthrough bleed in fitusiran studies[34]. Thus, the re-initiation of the OLE and ATLAS trials is expected around the end of the year 2017.

Concizumab

Another attractive haemostatic treatment targeted at rebalancing the coagulation system in haemophilia is

the suppression of tissue factor pathway inhibitor (TFPI), the main negative regulator of tissue factor (TF)-initiated coagulation[35]. Among the different pharmaceutical agents being investigated to inhibit TFPI, concizumab (Novo Nordisk), a humanised monoclonal antibody against TFPI, is the one at the most advanced stage of development[29]. Concizumab has a high affinity for the KPI-2 domain of TFPI (the binding site of FXa): by preventing FXa binding to TFPI, concizumab also prevents TFPI inhibition of the TF-FVIIa complex, resulting in enhanced tenase and thrombin formation[36]. In a rabbit haemophilia model, intravenous or subcutaneous concizumab significantly reduced cuticle bleeding, with an effect comparable to that of rFVIIa[37]. In a phase I randomised study (Explorer™1) conducted in 24 haemophilia A and B patients and 28 healthy volunteers, escalating single doses of concizumab (0.5-9,000 μg/kg intravenously or 50-3,000 μg/kg subcutaneously) produced detectable plasma levels of the monoclonal antibody for up to 43 days, with a reduction in TFPI plasma concentrations and functional activity for 14 or more post-dosing days[38]. There were no serious adverse events and no anti-concizumab antibody developed. In a multi-centre, open-label, multiple-dosing phase I clinical trial (Explorer™2), concizumab administered to 4 healthy males (250 μg/kg every other day for 8 doses) improved thrombin generation, with antibody plasma levels correlating directly with thrombin generation and inversely with TFPI levels[39]. In the same study, concizumab was added *ex vivo* to plasma from 18 individuals with severe haemophilia A or B (with or without inhibitors) restoring thrombin generation to near-normal levels[39]. A phase I, multi-centre, randomised, placebo-controlled, double-blind trial investigating safety, PK and pharmacodynamics (PD) of multiple doses (0.25, 0.5, 0.8 mg/kg every fourth day) of concizumab administered subcutaneously to haemophilia A patients (Explorer™3) has been recently completed[40]. No safety concerns emerged from this primary analysis, which also confirmed a PK/PD relationship among concizumab dose, TFPI levels and thrombin generation. In addition, a *post-hoc* analysis indicated concizumab exposure levels of at least 100 ng/mL as those most effective in reducing the frequency of bleeding episodes and thus more indicated for prophylaxis[40]. Two phase II trials evaluating the safety and efficacy of prophylactic administration of concizumab in haemophilia A and B with (Explorer™4, NCT03196284) and without (Explorer™5, NCT03196297) inhibitors are currently ongoing.

Conclusions

A better understanding of the molecular mechanisms of haemostasis, along with the need to develop more effective therapies to treat and/or prevent bleeding in patients with inhibitors, have prompted the development of innovative therapeutic strategies for haemophilia, based on mechanisms other than the replacement of the deficient coagulation factor.

Although acting by different mechanisms (emicizumab enhances coagulation activity and fitusiran and concizumab inhibit anticoagulant pathways), and being at different stages of clinical development (emicizumab has obtained FDA approval whereas fitusiran and concizumab are at phase II-III), these newer molecules are generally characterised by long half lives permitting infrequent dosing, subcutaneous administration, no immunogenicity against FVIII, and the capacity to improve thrombin generation independently from the degree of the coagulation factor deficiency or presence of inhibitors. Besides their primary use for the treatment or prevention of bleeding episodes in patients with haemophilia and inhibitors, trials are currently evaluating the impact of these innovative agents also in non-inhibitor haemophilia patients in order to improve patients' adherence to prophylaxis (and thus quality of life) and to reduce the occurrence of inhibitors in patients at high risk. The therapeutic need for non-replacement therapies is emphasised by a recent randomised trial that compared the immunogenicity of plasma-derived and recombinant FVIII products in previously untreated patients with severe haemophilia A and showed that, even though plasma-derived FVIII is less immunogenic than recombinant FVIII, the cumulative incidence of inhibitors following the infusion of the former products is still unacceptably high[41]. In this light, the potential use of products not based on FVIII replacement to treat or prevent bleeding in patients at risk of developing inhibitors is of great value. However, pivotal trials have taught us that no rose is without thorns. Indeed, the occurrence of thromboembolic complications during the use of emicizumab and fitusiran induced investigators to modify treatment protocols, in particular contraindicating the prolonged concomitant administration of aPCC.

In conclusion, there is no doubt that these newer agents have the potential to revolutionise haemophilia treatment, raising great expectations among both the medical and haemophilia patients' communities.

Disclosure of conflicts of interest

MF has no conflicts to disclose. PMM received fees from Bayer, Kedrion, Alexion, Baxalta/Shire, CSL Behring, Grifols, LFB, Novo Nordisk and Octapharma for lectures or participation on advisory boards.

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