Emicizumab for the treatment of haemophilia A: a narrative review

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Abstract

One of the most serious complications of the treatment of severe haemophilia A is the development of alloantibodies against exogenous factor VIII (FVIII). Inhibitors render factor replacement therapy ineffective, exposing patients to a remarkably 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 newer haemostatic therapies that are not based on the replacement of the deficient FVIII. This review will focus on the most interesting among these innovative therapies, emicizumab, and will provide an update on its current stage of clinical development.

Keywords: emicizumab, haemophilia A, inhibitors, bleeding.

Introduction

Haemophilia A arises from a mutation in the factor 8 (*F8*) gene resulting in the deficiency or dysfunction of clotting factor VIII (FVIII). Patients with plasma factor levels less than 1% of normal are classified as having severe haemophilia, those with levels of 1-5% of normal as moderate haemophilia, and those with levels over 5-40% of normal as mild haemophilia[1-4]. Patients with mild haemophilia bleed excessively only after surgery, tooth extractions or major injuries, whereas patients with moderate haemophilia bleed excessively even after relatively minor trauma. Those with severe haemophilia bleed spontaneously or after slight, otherwise insignificant trauma. The clinical hallmark of haemophilia A is intra-articular bleeding predominantly into knee, elbow and ankle joints[3]. Bleeding can also occur into other body tissues, including muscles, skin and mucous membranes in addition to joint bleeds. All these bleeding events are managed by replacement of the missing endogenous FVIII with an exogenous FVIII infusion[5-7]. Lyophilised plasma-derived FVIII concentrates first went into industrial production over 40 years ago. They allow the implementation of regular FVIII prophylaxis as a therapeutic regimen instead of episodic FVIII replacement at the time of bleeding, and represent the first major advance in the management of haemophilia A patients[8].

Following the cloning of the *F8* gene in 1982, replacement therapy for individuals with haemophilia A entered an exciting new era with the development of recombinant FVIII products (from first generation to the current long-acting recombinant FVIII products) able to combine technological solutions aimed at improving haemostatic efficacy and safety. In the last twenty-five years, the availability of a high standard of haemophilia care has greatly improved the quality of life of haemophilia patients, and, at least in developed countries, their life expectancy has reached that of males in the general population[9].

In this context, the most challenging complication in the treatment of haemophilia A today is the development of anti-FVIII alloantibodies, which affect approximately one-third of patients with severe haemophilia A. Inhibitors make traditional replacement therapy ineffective, prevent access to a safe and effective standard of care (particularly prophylaxis in children), and predispose them to an unacceptably high risk of morbidity and mortality[10,11]. The current management of bleeding episodes in haemophilia A patients with inhibitors includes the use of the bypassing agents activated prothrombin complex concentrate (aPCC) (Factor Eight Inhibitor Bypassing Activity-FEIBA, Shire pcl, Lexington, MA, USA) and recombinant activated factor VII (rFVIIa) (NovoSeven, Novo Nordisk, Bagsværd, Denmark)[10,12]. Due to the heavy social, health and economic burden represented by the use of inhibitors[13], it is not surprising that investigators have dedicated their research over the last decade to understanding the pathogenic mechanisms of inhibitors and to the development of even more effective haemostatic therapies[14-17]. In particular, the most recent research has been focused on newer therapies not based on FVIII replacement[17].

In this review, we summarise the current knowledge on emicizumab, one of the most interesting of these innovative haemostatic agents, and that which is currently at the most advanced stage of development.

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Search methods

We analysed the medical literature for published studies on the use of emicizumab in haemophilia A patients with inhibitors. The MEDLINE electronic database was searched without any time limitations, using 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 "inhibitors" AND "by-passing agents" AND "emicizumab" AND "ACE910" AND "haemlibra" AND "innovative therapies". We also screened the reference lists of the most important 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 and thrombosis and haematology.

Mechanism of action and development of emicizumab

Emicizumab (Roche, Basel, Switzerland) 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, thereby promoting FIXa-catalysed FX activation and tenase formation[18,19]. However, despite their remarkable similarity, recent analyses indicate that FVIII and emicizumab differ profoundly from each other in terms of affinity for the antigen, regulation, topology, and FIXa-enhancing activity[20]. The result of emicizumab-induced haemostasis is, therefore, a disruption of the natural physiological "on-off" switch mechanism with FVIII-induced haemostasis leading to a permanent "on" setting[20].

In a short-term primate model of acquired haemophilia A conducted by Muto *et al.*[21], single intravenous bolus administrations of 1-3 mg/kg emicizumab controlled artificially-induced muscle or subcutaneous bleeds to the same degree as recombinant porcine FVIII infused at twice-daily intravenous doses of 10 U/kg[22]. In a long-term primate model of acquired haemophilia A[23], the same authors showed that weekly subcutaneous doses of emicizumab (initially 4 mg/kg followed by 1 mg/kg) prevented bleeding episodes, including joint bleeding[23], making this agent potentially attractive for prophylactic use in haemophilia patients.

The first human trial of emicizumab was completed in 2015 on 64 healthy non-haemophilia male adults receiving a single subcutaneous injection of emicizumab up to 1 mg/kg bodyweight or placebo[24]. Emicizumab showed a linear pharmacokinetic profile in these healthy volunteers with peak plasma concentration occurring 1-2 weeks post injection and a half-life of approximately 30 days, regardless of the dosage group. In *ex vivo* FVIII neutralised plasma of the study participants, the bispecific antibody shortened activated partial thromboplastin time and increased peak height of thrombin generation in a dose-dependent manner. No serious adverse events were recorded[24]. A subsequent 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 *et al.*[25]. The study end points were safety and pharmacokinetic profiles, as well as the annualised bleeding rate (ABR). The authors observed a marked reduction in the median ABR, which decreased from 32.5 to 4.4 (0.3 mg/kg group), from 18.3 to 0.0 (1 mg/kg group), and from 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 FVIII inhibitors. No significant safety concerns were identified in this study.

Pivotal clinical trials

The pivotal clinical trials on the use of emicizumab in haemophilia A patients were designed as multicentre studies under the name HAVEN. So far, four phase III HAVEN trials have been completed (see Table I). A fifth HAVEN study (a randomised, open label phase III trial which evaluates safety, efficacy and pharmacokinetics of prophylactic emicizumab *vs* no prophylaxis in haemophilia A participants) is still ongoing.

HAVEN 1

The phase III open-label, multicentre, randomised HAVEN 1 trial was published in 2017, enrolling a total of 109 subjects aged >12 years with congenital haemophilia A and high-titre inhibitors[26]. The ABR was 2.9 events (95% confidence interval [CI]: 1.7-5.0) among participants who were 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 favor of emicizumab prophylaxis ($p<0.001$). Emicizumab prophylaxis resulted in a significant reduction in treated bleeds of 79% ($p<0.001$) compared to previous treatment with bypassing agent prophylaxis in a non-interventional study prior to enrollment[26]. Serious side effects, including thrombotic microangiopathy in three subjects and other thrombotic events in two subjects, were reported and were associated with cumulative doses of aPCC >100 U/kg/24 hours (h) administered for the treatment of breakthrough bleeds during emicizumab prophylaxis. No events were reported when emicizumab was given alone or in conjunction with rFVIIa alone[26].

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Table I - Main characteristics of the pivotal HAVEN trials on emicizumab in haemophilia A.

Study, year[ref]	Study design	Study population	Dosing	Main results	
				Efficacy	*Safety*
HAVEN 1, 2017[26]	Phase III randomised open-label	109 (adolescent and adult haemophilia A with inhibitors)	Loading dose: 3 mg/kg/week for 4 weeks Maintenance dose: 1.5 mg/kg/week	Emicizumab prophylaxis *vs* no prophylaxis resulted in an 87% reduction of ABR	5 SAEs (3 thrombotic microangiopathies and 2 thromboses)
HAVEN 2, 2017[27]	Phase III non-randomised open-label	60 (paediatric haemophilia A with inhibitors)	Loading dose: 3 mg/kg/week for 4 weeks Maintenance dose: 1.5 mg/kg/week, or 3 mg/kg every 2 weeks, or 6 mg/kg every 4 weeks	Emicizumab prophylaxis *vs* no prophylaxis resulted in a 99% reduction of ABR	No thrombotic events
HAVEN 3, 2018[28]	Phase III randomised open-label	152 (adolescent and adult haemophilia A without inhibitors)	Loading dose: 3 mg/kg/week for 4 weeks Maintenance dose: 1.5 mg/kg/week, or 3 mg/kg every 2 weeks	96% and 97% reduction in ABR in the two emicizumab arms, respectively, compared to episodic FVIII therapy	No major safety issues
HAVEN 4, 2017[29]	Phase III non-randomised open-label	48 (adolescent and adult haemophilia A with or without inhibitors)	Loading dose: 3 mg/kg/week for 4 weeks Maintenance dose: 6 mg/kg every 4 weeks	Efficacy results similar to HAVEN 1, 2, and 3	No major safety issues

ABR: annualised bleeding rate; SAEs: serious adverse events; FVIII: exogenous factor VIII.

HAVEN 2

The HAVEN 2 trial is a phase III open-label, multicentre, safety, efficacy and pharmacokinetic study of emicizumab prophylaxis in paediatric haemophilia A patients (<12 years of age and 12-17 years of age if under 40 kg) with inhibitors. The study is still ongoing and an *interim* analysis was recently presented in abstract form by Young *et al.*[27]. To date, 60 patients have been enrolled for whom data are available. Of the 57 patients aged <12 years, 54 (95%) experienced no bleeds requiring treatment; three patients experienced one bleed each requiring treatment, and all were effectively treated with rFVIIa. In total, 37 out of 57 patients (65%) reported no bleeds at all. A total of 65 bleeds were reported in 20 patients. For those patients on study with at least 12 weeks of follow up (n=23), the ABR for treated bleeds was 0.2 events/year (95% CI: 0.06-0.62). For the 13 patients for whom such analysis was possible, intra-patient comparison showed a 99% reduction in ABR for treated bleeds following initiation of emicizumab prophylaxis, compared with prior bypassing agents[27]. No cases of thrombotic microangiopathies or thromboembolic events were reported. The pharmacokinetics of emicizumab in this paediatric population were similar to those seen in the HAVEN 1 study in adolescents and adults[27].

HAVEN 3

The phase III HAVEN 3 trial is an open-label, multicentre randomised trial of emicizumab prophylaxis in patients with haemophilia A aged >12 years without FVIII inhibitors[28]. A total of 152 patients were enrolled and randomised into three arms: two on subcutaneous emicizumab prophylaxis and one on continuation of previous "on-demand" FVIII treatment. ABR of the emicizumab groups were 1.5 and 1.3, respectively, representing a 96% and 97% reduction in ABR compared to patients on episodic FVIII therapy (ABR: 38.2). The secondary outcome measure evaluated patients who had been on FVIII prophylaxis prior to switching to emicizumab prophylaxis; also in this fourth group there was a notable 68% reduction in ABR (from 4.8 to 1.5). Of note, no thromboembolic events were recorded in any patient during the study period[28].

HAVEN 4

The HAVEN 4 trial is a single-arm phase III study evaluating the prophylactic use of emicizumab in patients aged >12 years with congenital haemophilia A with or without inhibitors[29]. This study is still ongoing and has enrolled 48 patients. It involves a pharmacokinetic and an expansion phase and was designed to evaluate the safety and efficacy of an alternative dosing regimen of subcutaneous emicizumab (6 mg/kg once a month). Preliminary results, including ABR, efficacy and safety, were consistent with those of the three previous HAVEN studies[29]. In particular, 56% of patients with or without inhibitors receiving this regimen experienced no bleeds requiring treatment.

Emicizumab is currently registered under the name Hemlibra (Roche) in over 50 countries around the world for prophylactic use for haemorrhagic episodes in adult and paediatric haemophilia A

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patients with inhibitors[30]. In addition, this drug recently received the approval of the US Food and Drug Administration (FDA) also for prophylaxis in patients with haemophilia A without FVIII inhibitors. The recommended loading dose of emicizumab is 3 mg/kg by once-weekly subcutaneous injection for the first 4 weeks for all approved prophylactic dosing regimens. In addition to the already approved weekly dose of 1.5 mg/kg, the more recently FDA-approved Hemlibra maintenance dosing regimens includes 3 mg/kg by subcutaneous injection once every 2 weeks and 6 mg/kg by subcutaneous injection every 4 weeks[31].

Management of patients on emicizumab

The registration of emicizumab for clinical use has provided a significant insight into the treatment of haemophilia A patients with inhibitors. Physicians at haemophilia treatment centres now have the addition of an extraordinary weapon to their therapeutic armamentarium. However, although the introduction of this innovative haemostatic agent has drastically changed the management of these patients, in some cases, this might prove challenging for those treating haemophilia patients[32-36].

For example, the impact of emicizumab on laboratory monitoring of haemophilia A patients is a critical issue[37,38]. Although the current use of emicizumab does not require laboratory monitoring, this drug interferes with all clot-based assays leading to an unreliable measurement of activated partial thromboplastin time (APTT), FVIII activity, and FVIII inhibitor titre. These can be measured using chromogenic assays which are unaffected by emicizumab. Such tests are, however, costly and not easily available to all laboratories. A possible solution to this problem was recently proposed by Nogami *et al.*[39], who developed a methodology of adding two anti-emicizumab neutralising antibodies *in vitro* to eliminate the influence of emicizumab on the plasma-based assays that measure FVIII activity or FVIII inhibitor titre. Using this method, FVIII activity and FVIII inhibitor titre can be measured using clot-based assays even under emicizumab treatment. Global coagulation assays have been explored as potential solutions[40-42]. In addition, a commercially available assay has recently been developed to allow direct measurement of emicizumab activity[43].

Another important issue, which is closely linked to the safety aspects, is the management of bleeding episodes in haemophilia A inhibitor patients under emicizumab therapy. As previously mentioned, the most severe adverse events reported during the HAVEN 1 study were three thrombotic microangiopathies and two thromboses which all occurred in patients receiving high aPCC doses (>100 U/kg/24 h) concurrent to emicizumab[23]. None of the patients who developed thromboembolic events required anticoagulation, and improvement or resolution was documented in all cases within one month of aPCC being stopped[26]. Once mitigating measures were put in place (avoiding concurrent use of emicizumab and aPCC), no further microangiopathy or thrombotic events occurred during the ongoing HAVEN 1 or any of the other emicizumab clinical trials[44,45]. The United Kingdom Haemophilia Centre Doctors' Organisation (UKHCDO) has recently published a guideline[46] on the treatment of bleeding episodes in haemophilia A patients with FVIII inhibitor receiving emicizumab. The UKHCDO recommended that rFVIIA should be adopted as first-line treatment of bleeds, and that bleeding episodes should not be treated with aPCC unless no other option is available (in this case, an initial aPCC dose not exceeding 50 U/kg should be used). The same panel of experts also suggested using by-passing agent rFVIIa for the management of surgical procedures that cannot be delayed, for which very few data are available in the literature[46].

Conclusions

Emicizumab is a unique, novel molecule, and its wider prophylactic use is expected to have a real-life dramatic impact in reducing the bleeding frequency in the community of haemophilia A patients, significantly improving their clinical condition and, ultimately, their quality of life[47]. However, in order to maximise its therapeutic potential, clinical experience of using emicizumab needs to be widened in specific conditions, such as the combination with other haemostatic drugs, and the management of surgeries and bleeding events, particularly in the setting of congenital haemophilia A without inhibitors. More research is also needed to better characterise the mechanisms of action of emicizumab and its interaction with the proteins of the haemostatic system. Further trials are also required to assess the safety and efficacy of emicizumab prophylaxis to prevent bleeding episodes during immune tolerance induction. Finally, another unsolved question that needs to be addressed in the near future is the development of an effective assay to monitor emicizumab levels and treatment efficacy.

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Disclosure of conflicts of interest

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