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Emicizumab and thrombosis: the story so far

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Emicizumab is a recombinant, humanised bispecific monoclonal antibody that binds factor IXa and factor X. Although emicizumab mimics factor VIII, in that it enhances factor IXa-mediated factor X activation, its mechanism of action is not exactly the same. For instance, factor VIII requires activation before it can interact with factor IXa, and due to its intrinsic instability, factor VIIIa loses rapidly its cofactor function. It thus has an on/off-switch. Emicizumab has no such on/off switch, and is immediately ready for action as soon as factor IXa is available. Secondly, factor VIIIa is the limiting factor within the tenase complex (it has the lowest concentration, and it inactivates rapidly), whereas due to the molar excess of emicizumab, factor IXa is the limiting component in emicizumab-supported factor Xa generation. Finally, FVIIIa stimulates factor IXa activity via a number of different mechanisms [1], whereas emicizumab predominantly promotes factor IXa and factor X to be in close proximity. It is not surprising therefore that emicizumab is less efficient as a cofactor compared to factor VIIIa. However, it is important to keep in mind that this does not mean that emicizumab is unable to facilitate the production of similar amounts of factor Xa. Less efficient implies that more factor IXa/Emicizumab complexes are needed to activate similar amounts of factor X as will the tenase complex. As long as enough factor IXa is available (produced by factor VIIa/tissue factor or factor XIa, or infused as part of clotting factor concentrates), then sufficient factor IXa/emicizumab complex can be formed. Although it is currently unclear how much factor IXa is generated in the different tissues following different types of injury, the significant reduction in annual bleed rate (ABR) points to sufficient amounts of factor IXa/emicizumab complex being generated to control spontaneous bleeds.

Emicizumab is administered subcutaneously between once a week and once a month due to its half-life of almost a month. The HAVEN 1-4 research studies established its efficacy in haemophilia patients with and without inhibitors and granted licensure for use for bleeding prevention in Europe and North America as well as in an increasing number of other regions worldwide. At the registered emicizumab dose, patients achieve thrombin generation in the range of patients with mild haemophilia.

In terms of efficacy, the results have been impressive in reducing the annual bleed rate especially in patients with alloantibodies to FVIII (inhibitors). In individuals with haemophilia A without inhibitors, the efficacy is similar to that of well-controlled prophylaxis with the advantage of subcutaneous once weekly or less frequent dosing rather than intravenous injection two to three times a week. The issues of what level of physical activity can be safely performed and how to manage the peri-surgical risk of bleeding remain to be defined.

In terms of safety, the most common adverse events are injection site skin reactions, which have been reported in up to 15% of patients [2]. These are usually mild and self-limiting with most patients continuing on the emicizumab despite these reactions.

More important however are the episodes of thrombosis, thrombotic microangiopathy (TMA) and death, which will be discussed in this commentary. The first reports of thrombotic complications came from the HAVEN 1 trial where three patients developed TMA, two developed thrombosis and one patient died [2].

Thrombotic microangiopathy

TMA is a very rare, life-threatening condition and in the form of thrombotic thrombocytopenic purpura (TTP) it is associated with congenital or acquired deficiency of ADAMTS 13. The incidence of TTP in the general population is approximately 10 in a million per year [3]. TMA has rarely been observed in haemophilia patients undergoing factor replacement therapy [4]. Thus, the development of this complication in 3 of 109 patients in the HAVEN 1 trial was immediately perceived as unlikely to be a chance occurrence. All the affected patients developed thrombocytopenia, and displayed laboratory markers of haemolysis and fragmented red cells on the peripheral blood film while maintaining normal ADAMTS13 levels, configuring the picture of atypical TTP. A detailed analysis of the TMA cases showed that they were all exposed to FEIBA at doses of over 100units per Kg per day, given to treat acute bleeding episodes during emicizumab prophylaxis. In contrast, no episodes were observed when rFVIIa was used to treat the acute bleeding episodes. In explaining the difference between FEIBA and rFVIIa in triggering TMA in patients on emicizumab, it is worth noting that FEIBA contains factors IX/IXa as well as X/Xa, which are the substrates for the bispecific antibody. Since Emicizumab does not require activation to exert its cofactor function, an excess of factor IXa may lead to uncontrolled thrombin generation and the resulting thrombotic complications. Only very limited information is available on the episodes of thrombosis that occurred outside HAVEN 1 [5]. One further episode of TMA has been reported in the post marketing setting [5]. In contrast to the clinical course of classical TTP, the microangiopathy in these individuals resolved rapidly following discontinuation of the FEIBA treatment. In at least one of the cases, it was possible to resume emicizumab and treat bleeds with rFVIIa without recurrence of the TMA.

Venous and arterial thrombosis

Seven thrombotic events have been reported of which three were venous, one was arterial while the locations of the remaining three events have not been reported. Two of the venous thromboses were reported in HAVEN 1. One was a right saphenous vein thrombosis after two doses of FEIBA to treat joint and right shin bleeds on consecutive days; the patient applied an ice pack to the shin bleed and developed extensive skin necrosis over the area. Another patient developed cavernous sinus thrombosis after receiving FEIBA to treat a joint bleed. Both of these patients with thrombosis received concomitant treatment with FEIBA at a dose of >100u/kg/day. After resolution of the cavernous sinus thrombosis the patient restarted emicizumab with no further problems and uneventfully received rFVIIa to treat joint bleeds and a dental procedure [2].

Deaths

A total of 10 deaths have been reported so far in patients on emicizumab. Clinicians who cared for 2 of the patients in the compassionate use program reported that those deaths were unrelated to the emicizumab. The haemophilia A patient with an inhibitor in the HAVEN 1 trial died from rectal bleeding; he refused a blood transfusion and the death was considered to be unrelated to the drug. A point for consideration however, is that the use of emicizumab limits the use of other treatments such as FEIBA. It cannot be excluded that under such conditions, the use of emicizumab prevents the application of FEIBA, which could be used to control bleeding.

We have insufficient information on the other seven deaths to judge whether or not emicizumab could have played a role. Whilst we understand the need to protect privacy, we feel that the current listing of the deaths at www.emicizumabinfo.com [5] without details about the causes or at least circumstances is of suboptimal utility, and we recommend the manufacturer to explore options to expand the information provided to include, as a minimum, the cause of death and the patient's inhibitor status.
The manufacturer states that there are currently 2500 haemophilia A patients with and without inhibitors being treated with emicizumab. This would give a raw mortality rate of 4/1000 treated patients. We cannot judge whether this is the expected rate, or is higher/ lower than expected, as we do not have the critical information needed for a proper appraisal. Indeed, we do not know the demographics of the patients and the length of exposure to emicizumab, as well as the "control" mortality rate in patients treated with bypassing agents or factor concentrates but without emicizumab.
As the number of emicizumab users increases, it is likely that the number of deaths will increase. It is difficult to predict if more or less of them will be reported, but the quest of the community to find out whether or not there is an excess of deaths on emicizumab is unlikely to fade away. Therefore, we suggest the manufacturer establishes an independent panel to examine the drug-relatedness of all the adverse events, including deaths, and to set up studies that will help to generate the evidence needed to answer this question.

Acquired haemophilia

Emicizumab is only licensed for patients with congenital haemophilia A with and without inhibitors. The efficacy and relative safety of emicizumab in the HAVEN 1, 2 and 4 trials led some clinicians to start using it off license in patients with acquired haemophilia despite the lack of published efficacy and safety data. The dose and frequency used have been the same as those licensed for congenital haemophilia and inhibitors. We expect the number of patients with acquired haemophilia who have been exposed to emicizumab to be very small, but despite this, one patient developed pulmonary emboli, one had a thrombotic stroke and a third patient died suddenly (Table 1). Even against the relatively high death rate in acquired haemophilia in general [6], three deaths in a very small series of treated cases is an alarming figure. The safety profile of this drug in acquired haemophilia remains to be established, and patients should not be exposed to emicizumab for this indication outside clinical trials. There are good reasons for the thrombotic risk being higher in this group, as older age, autoimmunity, and cancer, which are risk factors for acquired haemophilia, are also risk factors for thrombosis. Furthermore, patients with severe haemophilia produce no or very little FVIII, whilst acquired haemophilia patients produce large amounts of FVIII which is initially neutralised by the autoantibody but later, as the immunosuppression kicks in, becomes available in the circulation and often reaches supra normal levels. These features suggest that if this drug is used in clinical trials in patients with acquired haemophilia, the dose may need to be lower and more closely monitored so that the treatment is stopped as the endogenous FVIII starts to rise.

The use of concomitant rFVIIa

In the current issue of the Journal of Thrombosis and Haemostasis, Levy and colleagues present the data on bleeds in patients on emicizumab that were treated with rFVIIa in the Haven 1, 2 and 4 clinical trials [7]. A total of 61 patients with congenital haemophilia A and inhibitors were treated for a total of 210 bleeds with rFVIIa. No thromboses or TMAs were observed in these patients. It should be noted, however, that patients with a high risk of thrombosis were excluded from entering these trials in the first place and not many of the rFVIIa treatments were used in the settings of sepsis, surgery or major trauma. Furthermore, around half of the rFVIIa exposures were single dose treatments.

Monitoring of adverse events

Adverse event monitoring is an essential component of studies in all phases of development of new drugs and observed cases are included in trial publications. Adverse events should also be reported to national systems available for reporting events on any medication, as well as to multicenter/multinational databases such as the European EUHASS, Canadian BDR and US ATHEN haemophilia specific systems. In our view clinicians should also be permitted to openly report adverse events in clinical trial patients once a drug has been licensed. Currently confidentiality agreements in clinical trial contracts prevent clinicians from reporting adverse events to independent adverse event databases. Whilst it is reasonable not to disclose events during phase III randomized double-blind clinical trials, which are overseen by dedicated drug safety monitoring boards (DSMB), open reporting and disclosure should be adopted for licensed drugs in post-marketing trials, particularly when drugs are prescribed as part of usual care after licensure.

In the case of emicizumab, a website [5] presenting the cumulative adverse event data reported to all sources has been made available as an open access resource to US physicians by Genentech (part of Roche, the manufacturer of emicizumab). The site is updated every three months and contains data from throughout the world, but unfortunately it has not been open to other regions of the world. Another issue with the website is that, while it clearly displays the cumulative data, details of the specific events, especially in the case of deaths, are limited. This, in turn, makes it difficult to impossible to independently assess the likelihood of a causal link between emicizumab administration and the reported adverse event. With regard to causality assessment, because emicizumab has a long half-life, adverse events up to 3 months after discontinuation of the drug should be reported. This is of particular importance when emicizumab is temporarily discontinued in the setting of elective major surgery in inhibitor patients where full dose FEIBA may be used to cover the surgery. Finally, contextual reporting of the cumulative population exposure to emicizumab (at least in terms of estimated treatment years) should be posted to provide a denominator to the events.

Conclusion

Emicizumab has shown marked efficacy and relative safety in clinical trials and is now licensed in Europe and North America. The thrombotic events in the trials occurred when patients also received FEIBA at a dose greater than 100u/kg/day. Although the data suggest that rFVIIa is safer than FEIBA when used in patients on emicizumab, more data on its use

especially in the context of sepsis, surgery and major trauma are required. It is not known if the deaths of ten patients taking emicizumab represent a higher than expected death rate, and prospective observational studies should be set up to answer this question. In the meantime, all adverse events but particularly TMA, thrombosis and deaths of patients taking or having recently discontinued emicizumab should be reported to the relevant authorities and databases.

Declaration on interests

MM is the project lead for the EUHASS project on adverse event reporting in haemophilia in Europe and since 2018 the project received approximately 10% of its funding from Roche. MM and AI are PIs in the Stacey study. AI's institution, McMaster University, has received research funding from Roche but he has not received personal honoraria or reimbursements. PL has had honoraria, speaker fees or consultancies from LFB, Roche, Takeda/Shire, Sobi, Catalyst Biosciences, Spark Therapeutics, Sanofi/Bioverativ, Bayer, CSL Behring, Kedrion, and Octapharma. He is the co-owner of Laelaps Therapeutics.

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Source	Patients	Age yrs	Venous thrombosis	Arterial thrombosis	Total thrombosis	Thrombotic microangiopathy	Deaths	Death details
HAVEN 1 [1]	109 (inhibitor)	>12	2	0	2	3	1	TMA +bleeding
HAVEN 2 [8]	88 (inhibitor)	<12	0	0	0	0	0	
HAVEN 3 [9]	152 (non-inhibitor)	>12	0	0	0	0	0	
HAVEN 4 [10]	48 with or without inhibitor	>12	0	0	0	0	0	
HOHOEMI [11]	13 (inhibitor)	<12	0	0	0	0	0	0
STACEY (f) [5,12]	195 (inhibitor)	>12	1		1	0	1	
Compassionate use [5]	Not disclosed	Any	0	0	0	0	3	Sepsis, Cerebral bleed, Pseudotumour bleed
Expanded access [5]	Not disclosed	Any	0	0	0	0	1	
Post-marketing [5]	Unknown	Any	2		2	1	3	
Post-marketing acquired haemophilia [5, 13,14]	Unknown	Any	1	1	2	0	1	Sudden death
Total [5]	2500				7	4	10	

Compassionate use is the availability of the unlicensed drug to individuals assessed on a case by case basis provided certain criteria (such as no satisfactory approved alternative) are met. Expanded access is the availability of the drug to intermediate and large numbers prior to approval [5].