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Cover Page Footnote

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Emicizumab-kxwh: A Critical Review

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ABSTRACT

The first descriptions of haemophilia A were reported in the second century AD, with the first modern description by John Conrad Otto in 1803. Historically, the natural history of haemophilia A was associated with very high rates morbidity and mortality, often following trivial accidents. Although treatment options for haemophilia A have been revolutionised in recent decades, haemophilia A remains a hereditary disease of concern and factor replacement products remain the mainstay of treatment.

As such, patients with haemophilia can carry huge burdens, particularly when a complication such as a FVIII inhibitor is present. A recently approved novel therapeutic, Emicizumab-kxwh, has offered an unexpected and alternative approach to haemophilia A therapy. This recombinant, humanized, bi-specific antibody provides patients with effective haemostasis, empowerment of self-administration, and an overall improved quality of life. For patients with FVIII inhibitors, Emicizumab-kxwh offers a simple treatment mechanism that can efficiently overcome deleterious antibodies as the antibody bridges FIX and FX, mimicking the function of FVIII without sharing structural homology or biochemical properties. Considering this, the literature and clinical trials available to date have been critically analysed and discussed herein. This review aims to explore the advantages, disadvantages, and any potential need for caution with Emicizumab-kxwh.

INTRODUCTION

Haemophilia A is an X-linked coagulation disorder characterised by quantitative or qualitative defects in coagulation factor VIII (FVIII), also known as the antihaemophilic factor. This disorder is thought to have been reported as early as the second century AD (Franchini and Mannucci, 2014). However, modern descriptions were observed in the 1800's when it was noted that males from the same family (known as 'bleeders') suffered from several bleeding events with apparent asymptomatic female transmission (Schramm, 2014). The disease was not well understood at the time, but it was determined that males should not be circumcised if two brothers of the family had already died from excessive bleeding following the procedure (Franchini and Mannucci, 2014). The Babylonian Talmud indicates that if a woman has lost her first two sons after circumcision, she is exempt from the obligation to have the third son circumcised (Rosendaal, Smit and Briët, 1991). Haemophilia is commonly referred to as the royal disease, as Queen Victoria was a carrier of Haemophilia B which lead to several royal family members being affected by the disease (Franchini and Mannucci, 2014). One of the first clinically accurate descriptions of haemophilia A was reported in 1803 by John Conrad Otto. His understanding of the disease was "*if least scratch is made on the skin of some of them, as mortal a haemorrhage will eventually ensue*." He also was capable of observing the inheritance pattern by stating that "*it is a surprising circumstance that the males only are subject to this*

strange affection, and that all of them are not liable to it" (Otto, 1803). The first descriptions of the genetics of haemophilia were published in 1820 by Nasse culminating in Nasse's law, which states that haemophilia is transmitted entirely by unaffected females to their sons (Nasse, 1820).

Today, haemophilia A can be classified based on the severity of the FVIII deficiency present. Patients with mild haemophilia present with 5 - 40% of normal FVIII levels (>0.05-0.4 IU/mL); moderate haemophilia A with 1-5% of normal FVIII levels (0.01-0.05 UI/mL); and, severe haemophilia A with <1% of normal FVIII levels present (<0.01 IU/mL) (Bolton-Maggs and Pasi, 2003). Approximately 50-60% of patients with haemophilia A present with severe disease.

The qualitative or quantitative defects in coagulation FVIII observed in haemophilia A are hereditary. Genetic mutations in the FVIII gene, found on the long arm of the X chromosome at position Xq28, are responsible for this hereditary disease. Although more than 2800 different mutations of the *F8* gene are documented in the Human Gene Mutation Database, the most common mutation identified in haemophilia A is the intron 22 inversion (Inv22) of the *F8* gene, observed in 45% of severe haemophilia A patients (Bolton-Maggs and Pasi, 2003). Inv22 is a result of homologous intrachromosomal recombination between the *F8A* gene in intron 22 and two additional transcribed copies of the *F8A* gene telomeric and upstream to the *F8* gene (Lakich *et al.*, 1993; De Brasi and Bowen, 2008). While this is a hereditary disorder, it is noteworthy that Srivastava *et al.*, (2020), report that approximately 30% of cases of haemophilia, including instances of haemophilia B, arise as a result of spontaneous genetic variants.

The clinical significance of Haemophilia A is demonstrated by the spontaneous bleeding episodes often encountered by these patients. Haemophilia A patients (particularly those with these severe type), can suffer bleeding into joints (haemarthrosis) and soft tissues, muscle haematomas, gastrointestinal bleeding, central nervous system bleeding and excessive bleeding following trauma or surgery (Mansouritorghabeh, 2015; Srivastava *et al.*, 2020) Haemarthrosis is characteristic of the severe form of haemophilia A and is most seen in the knees, elbows, ankles and wrists (Mansouritorghabeh, 2015). Both haemarthrosis and muscle haematomas can lead to restricted movements in the joints and limbs affected (Mansouritorghabeh, 2015). Historically, these episodes could even be fatal for the patient as there were little or no treatment options available (Schramm, 2014). In the 1950's and 1960's, patients could be treated with fresh plasma. However, this form of therapy did not offer sufficient FVIII to treat serious bleeds, and fatalities were common (Franchini and Mannucci, 2014). At the time, this plasma was not treated with pathogen reduction techniques. Subsequently, many mortalities were seen because of human immunodeficiency virus (HIV) infection and hepatitis virus infections (Franchini and Mannucci, 2014).

However, today there are several safe treatment options available for haemophilia A patients. The most common treatments utilised are recombinant FVIII concentrates that have been available since the 1990s (Casademunt *et al.*, 2012). These FVIII concentrates act as a replacement for the deficient or defective physiological FVIII. These have been successful in reducing the rate of bleeding in haemophilia A patients by 90% (Morfini and Marchesini, 2020). Despite their success, these FVIII concentrates have still been associated with breakthrough bleeding when used as a prophylaxis. The annual bleeding rate (ABR) for patients using FVIII concentrates as a prophylaxis varies from 0-11.8 events per annum (Sun *et al.*, 2021). A study conducted by Musso *et al.*, 2008, observed that 65.7% of patients (mainly with

severe haemophilia A) using FVIII concentrates as prophylaxis experienced some form of spontaneous bleeding. However, this study also reports that 85.4% of bleeding events can be successfully treated with one or two infusions of FVIII concentrates. The most notable issue associated with these FVIII concentrates is the development of antibodies/inhibitors against them. Twenty percent of haemophilia A patients will develop an inhibitor against FVIII concentrate treatments, mainly in patients with severe haemophilia A (Walsh *et al.* , 2015; Paisley and Wight, 2003). These inhibitors can render treatment 2-3 times more expensive by comparison to those who do not develop an inhibitor (Guh *et al.*, 2012). More clinically significant, the presence of inhibitors means that bleeding episodes are more difficult to prevent and treat using FVIII concentrates.

With the above taken into consideration, FVIII concentrates have provided a considerable treatment option for haemophilia A patients. However, their drawbacks revealed a space on the market for a more efficient drug with a potentially easier administration. The relatively new bispecific antibody emicizumab-kxwh (HEMLIBRA, Genentech, Inc.) meets these requirements.

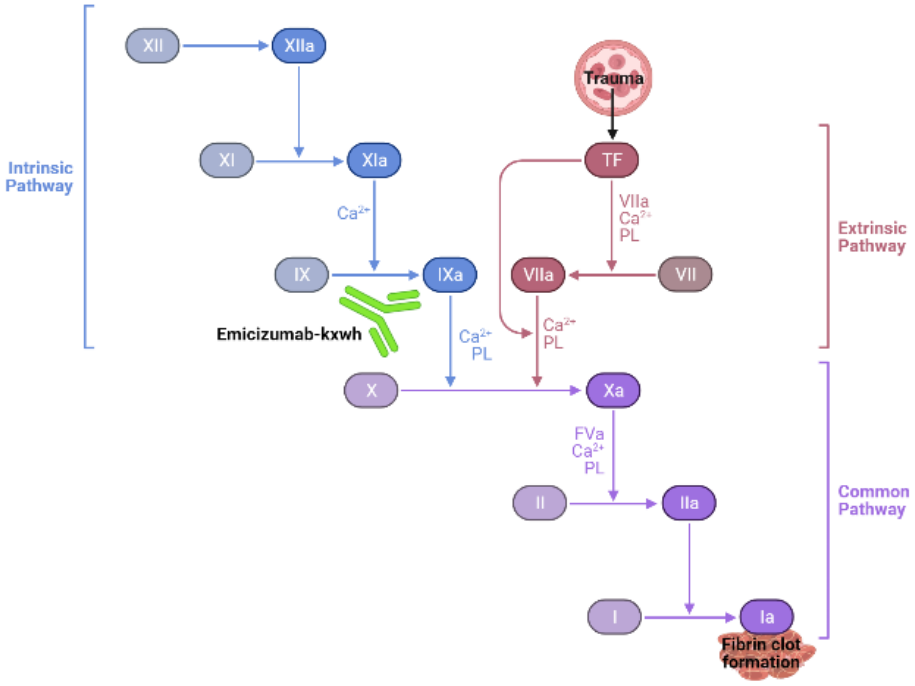
PHARMACODYNAMICS OF EMICIZUMAB-KXWH

The function of active FVIII (FVIIIa) *in vivo* is to act as a non-enzymatic cofactor for FIXa for the activation of FX in the presence of phospholipids and calcium ions (Mazurkiewicz-Pisarek *et al.*, 2016). This is part of the intrinsic coagulation pathway that leads to further activation of prothrombin to thrombin and subsequently allow for clot formation when fibrinogen converts to fibrin. Therefore, in haemophilia A, this mechanism is decreased or lost.

Emicizumab-kxwh (sold under the brand name HEMLIBRA) developed by Genentech, Inc. is a bispecific antibody that binds to both FIXa and FX, allowing it to mimic the function of FVIII to maintain haemostasis (Kitazawa *et al.*, 2017). The function of the antibody is based on the mechanism by which FVIIIa interacts with both FIXa and FX, as shown Figure 1 (Kitazawa *et al.*, 2017). Despite mimicking the function of FVIII, emicizumab-kxwh does not display structural homology with physiological FVIII or FVIII concentrates. This property allows it to evade the immunogenicity of inhibitors against FVIII that may be present in haemophilia A patients (Le Quellec and Negrier, 2018). FVIII and emicizumab-kxwh also have different biochemical properties (Müller *et al.*, 2019). Emicizumab-kxwh binds specifically to the EGF1 domain of FIXa and the EGF2 domain of FX, despite this domain being present in other vitamin K dependent factors (European Medicines Agency, 2018).

The route of administration for emicizumab-kxwh is subcutaneous (Yoneyama *et al.*, 2018) which is advantageous over intravenous administration (as seen with FVIII concentrates) as it allows for self-administration (Le Quellec and Negrier, 2018). There are a variety of dosing regimens available (1.5 mg/kg, 3 mg/kg or 6 mg/kg) which means emicizumab-kxwh can be administered weekly, fortnightly or monthly (Blair, 2019). This is highly convenient rather than administering intravenous FVIII concentrates two to three times per week, depending on the dosing regimen of FVIII required (Srivastava *et al.*, 2020). However, this strict regimen is necessary for FVIII concentrates due to their short half-life (Parisi and Kumar, 2021). In contrast, emicizumab-kxwh has a half-life of approximately 30 days and a high bioavailability following subcutaneous administration (Yoneyama *et al.*, 2018).

(a)



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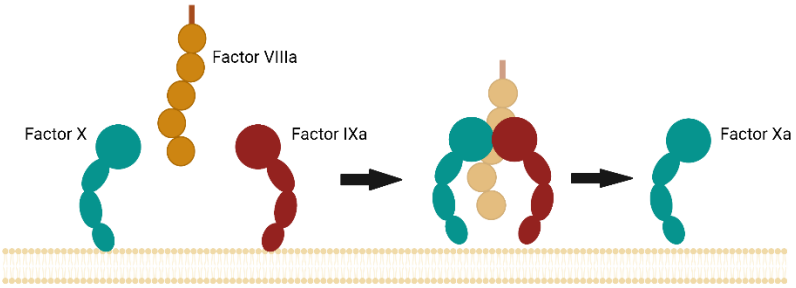

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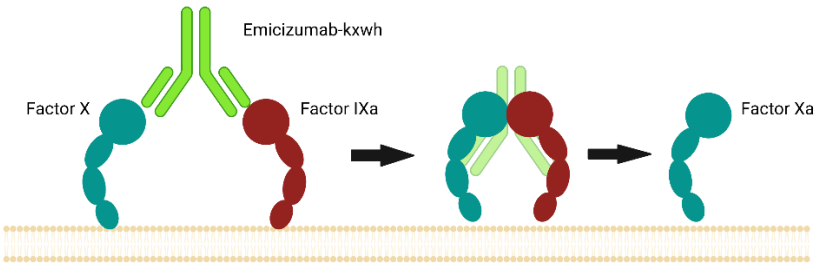

Figure 1: (a) Schematic representation of the mechanism of action of emicizumab-kxwh in the physiological coagulation cascade. ***(b)*** *Mechanism of action of physiological FVIII in vivo.* ***(c)*** *Mechanism of action of emicizumab-kxwh. Adapted from BioRender.com (https://biorender.com/).*

EFFICACY OF EMICIZUMAB-KXWH

Several studies have been conducted on the efficacy and safety of Emicizumab-kxwh in patients see table 1. HAVEN 1 successfully demonstrates that emicizumab-kxwh is capable of significantly reducing the ABR in comparison to haemophilia A patients receiving no prophylaxis. The ABR for treated bleeds was 2.9 in those receiving 1.5 mg/kg per week whereas the ABR for those receiving no prophylaxis was 23.3, an increase of 87% (Oldenburg *et al.*, 2017). However, most haemophilia A patients will receive some form of treatment so those receiving no prophylaxis do not fairly represent the 'normal' population. It was interestingly noted that participants in this trial who had previously been treated with episodic bypassing agents had an ABR of 37.7 (21.6 of which were treated bleeds). This then decreased to an ABR of 4.1 (1.7 of which were treated) when using emicizumab-kxwh. These ABR values were obtained in the first 24 weeks of the trial, and significant changes were seen in the long term. After one year of using emicizumab-kxwh, the ABR for participants was 0.6, 0 of which were treated bleeds (Oldenburg *et al.*, 2017). This indicates that emicizumab-kxwh may be a more effective prophylaxis in the longer term.

HAVEN 2 reported similar findings regarding the efficacy of emicizumab-kxwh in paediatric patients with inhibitors. However, this study investigated different dosing regimens of the drug and found that 3 mg/kg per 2 weeks appeared to be the most efficient. Participants receiving 3 mg/kg per 2 weeks had an ABR of 1.5 (0.2 of which were treated). Those receiving 6 mg/kg per 4 weeks had an ABR of 3.8 (2.2 of which were treated) and those receiving 1.5 mg/kg per week had an ABR of 3.2 (0.3 of which were treated) (Young *et al.*, 2019). However, caution should be taken when interpreting these ABRs as the higher ABR reported in the group of participants receiving 6 mg/kg per 4 weeks was primarily associated with two participants: one had several joint bleeds, and the other participant developed anti-drug antibodies (ADA). Interestingly, these ADAs had neutralising potential and there was very little emicizumabkxwh detectable in this participants bloodstream (Young *et al.*, 2019). In total, four participants developed ADAs as part of HAVEN 2. Two of these participants had ADAs without neutralising potential, which did not have any effect on the efficacy of the drug. However, the other two participants developed ADAs with neutralising potential. One of these participants had to drop out of the study with many bleeding events reported (as mentioned above). However, the other participant had decreased (but still detectable) levels of plasma emicizumab-kxwh. This participant had a 'normal' APTT and reported no bleeding events throughout the study, despite the presence of ADAs with neutralising potential. Follow up after the study showed that this participant had become ADA-negative and normal plasma emicizumab-kxwh levels were reported (Young *et al.*, 2019). To date, no clear predisposing factors for the development of ADAs in these participants has been identified.

Unlike HAVEN 1 and HAVEN 2, HAVEN 3 studied the efficacy of emicizumab-kxwh in participants without inhibitors. All participants of this study had previously received prophylactic or episodic FVIII concentrates (Mahlangu *et al.*, 2018). This study showed similar findings to HAVEN 1 as 56% and 60% of participants receiving 1.5 mg/kg per week and 3 mg/kg per 2 weeks, respectively, had no treated bleeding events whereas all participants (n=18) receiving no prophylaxis reported treated bleeds in the first 24 weeks of the study. HAVEN 1 showed that there was an 87% increase in treated bleeds when receiving no prophylaxis compared to when receiving emicizumab-kxwh in the first 24 weeks of the study. This study is a useful comparison of emicizumab-kxwh and FVIII concentrates efficacy as it includes

intraindividual analysis. Mahlangu *et al.*, (2018), report that the ABR decreased by 68% when a participant moved from FVIII prophylaxis to emicizumab-kxwh prophylaxis.

HAVEN 4 was a smaller study that focused on the 6 mg/kg per 4 weeks dosing regimen in mainly adult participants. This study reported that the ABR for participants after 24 weeks of emicizumab-kxwh was 4.5 (2.4 of which needed to be treated) (Pipe *et al.*, 2019). Interestingly, this study also states that 100% of the participants prefer emicizumab-kxwh over their previous treatment of intravenous FVIII (Pipe *et al.*, 2019).

While other studies were and continue to be carried out, the results obtained in HAVEN 1, HAVEN 2, HAVEN 3 and HAVEN 4 were vital in the approval of this drug for routine prophylactic use, as they were the largest clinical trial programmes for haemophilia A to date (Young *et al.*, 2019). Additional studies include HAVEN 5, HOHOEMI (Shima *et al.*, 2019) and STASEY. Results observed in the HOHOEMI study correlate with other paediatric studies such as HAVEN 2 and confirm the safety of emicizumab-kxwh for routine use. The HOHOEMI study also revealed that participants could participate in physical activity with moderate or high risk while maintain a low ABR (Shima *et al.*, 2019). Historically, high risk physical activity was a risk for haemophilia A patients and activities such as swimming, walking, rowing, sailing, and table tennis were encouraged (Srivastava *et al.*, 2020).

Table 1: Summary of Emicizumab-kxwh clinical trials

Name of study	Participants enrolled	Emicizumabkxwh dose investigated	Number of participants	Current status	References
HAVEN 1	Adults and adolescents with inhibitors	1.5 mg/kg per week	109	Completed	(Oldenburg *et al.*, 2017)
HAVEN 2	Children with inhibitors	1.5 mg/kg per week 3 mg/kg per 2 weeks 6 mg/kg per 4 weeks	88	Completed	(Young *et al.*, 2019)
HAVEN 3	Adults and adolescents without inhibitors	1.5 mg/kg per week 3 mg/kg per 2 weeks	152	Active, not recruiting	(Mahlangu *et al.*, 2018)
HAVEN 4	Adults and adolescents with or without inhibitors	6 mg/kg per 4 weeks	41	Active, not recruiting	(Pipe *et al.*, 2019)
HAVEN 5	Adults and adolescents with or without inhibitors	1.5 mg/kg per week 6 mg/kg per 4 weeks	70	Active, not recruiting	No results available
HOHOEMI	Children without inhibitors	3 mg/kg per 2 weeks 6 mg/kg per 4 weeks	13	Completed	(Shima *et al.*, 2019)
STASEY (Safety study)	Adults and adolescents with inhibitors	1.5 mg/kg per week	193	Completed	(HoffmannLa Roche, 2021a)

CURRENT GUIDELINES FOR THE USE OF EMICIZUMAB-KXWH

Emicizumab-kxwh is a relatively new haemophilia A therapy and has only been approved for routine use in recent years. Emicizumab-kxwh is Food and Drug Administration (FDA)

approved for routine prophylaxis in adult and paediatric patients with congenital haemophilia A and with inhibitors since November 2017, and without inhibitors since October 2018 (U.S. Food & Drug Administration, 2018). In Europe, the drug is approved for use by the European Medicines Agency (EMA) in haemophilia A patients with inhibitors since February 2018 and for patients with severe haemophilia A without inhibitors since January 2019 (Krumb *et al.*, 2021).

With three dosing regimens of emicizumab-kxwh available, there are variations seen between countries on the guidelines employed. The World Haemophilia Federation recommend that emicizumab-kxwh should be used for haemophilia A patients with an inhibitor and can be used for patients without an inhibitor (Srivastava *et al.*, 2020). Most countries recommend a loading dose of 3 mg/kg per week for four weeks, followed by a maintenance dosing regimen (Hoffmann-La Roche, 2021; European Medicines Agency, 2018). The maintenance dose is often based on physician and patient / caregiver preference in terms of adherence to the regimen (Holstein *et al.*, 2020). However, some countries have individual dosing recommendations for certain patient cohorts. For example, in Canada, all three dosing regimens (1.5 mg/kg per week, 3 mg/kg per 2 weeks and 6 mg/kg per month), are available. However, the 6 mg/kg per 4 weeks regimen is not recommended for paediatric patients or patients weighing <40 kg (HoffmannLa Roche, 2021). In contrast, the FDA recommend the standard loading dose followed by 1.5 mg/kg per week in the USA (U.S. Food & Drug Administration, 2017). In Ireland, the Health Products Regulatory Authority has authorised the use of 150 mg/ml and 30 mg/ml solutions that can be used to administer dosing regimens of 1.5 mg/kg per week, 3 mg/kg per two weeks or 6 mg/kg per four weeks (Irish Haemophilia Society, 2021).

LABORATORY TESTING FOR PATIENTS ON EMICIZUMAB-KXWH

FDA and EMA approval of emicizumab-kxwh will inevitably lead to an increase in patients using the drug in the future. This novel drug will likely inflict challenges in clinical laboratories associated with the monitoring of these patients (Srivastava *et al.*, 2020). Tests that have been shown to be affected by this drug include the activated partial thromboplastin time (APTT), the Bethesda clotting-based assay, APTT-based factor assays and activated protein C resistance assays. As expected, prothrombin time (PT) assays, thrombin time (TT) and chromogenic factor assays using bovine coagulation factor reagents remain unchanged in haemophilia A patients prescribed emicizumab-kxwh (Mahlangu *et al.*, 2018).

The APTT is a two-stage assay that can be used as a screening test for haemophilia A and other coagulation disorders, as well as an assay to monitor drugs such as unfractionated heparin (Lippi and Favaloro, 2019). It is a simple and cost-efficient assay that has easily lent itself to automation (Ignjatovic, 2013). The principle of the assay involves detection of a fibrin clot once the coagulation cascade of patient plasma has been activated by a FXII activator and calcium chloride. The results are reported in seconds, which is the time to clot formation (Ignjatovic, 2013). This should be carefully interpreted in patients with a haematocrit >55%, which is common in paediatric patients, as these patients have a decreased plasma volume, and the APTT may be increased consequently (Srivastava *et al.*, 2020). In this situation, the blood-to-anticoagulant ratio may need to be altered for accurate results.

Since haemophilia A affects FVIII, haemophilia A patients generally have a prolonged APTT (Srivastava *et al.*, 2020). In theory, emicizumab-kxwh should affect the results of any assay

that measures FIX or FX. Patients using emicizumab-kxwh have been reported to have a shortened APTT, some even within the 'normal' range (Bowyer, Kitchen and Maclean, 2020). This shortened APTT can be seen for as long as 6 months post emicizumab-kxwh treatment due to the long half-life of the antibody (Uchida *et al.*, 2016). Haemophilia A patients using FVIII concentrates also experience a shortened APTT result. However, the shortening affect caused by emicizumab-kxwh is more pronounced and can be evident with subtherapeutic levels of emicizumab-kxwh because emicizumab-kxwh does not require activation for function as FVIII concentrates do (Shimonishi *et al.*, 2020; Srivastava *et al.*, 2020).

Despite the widespread use of the APTT assay in laboratories, shortcomings are seen in terms of standardisation. Unlike the prothrombin time assay, the APTT is reported in seconds, regardless of what reagents are used. This can lead to varying results between laboratories and subsequently, results can be difficult to interpret (Ignjatovic, 2013). An example of this was seen when the APTT of several patients using emicizumab-kxwh was analysed using different reagents namely Actin, Actin FS, Actin FSL, Pathromtin SL, Synthasil, Synthafax, APTT SP, STA- PTTA, Cephascreen, CK Prest, Triniclot APTT S, Triniclot ATT HS and Triniclot APTT Auto. The APTT results obtained varied, with only eight out of thirteen reagents displaying a constant 'normal' APTT (Bowyer, Kitchen and Maclean, 2020). For this reason, the variability in reagents used in the APTT assay should be considered.

The Bethesda clotting-based assay is a useful method to identify the presence of FVIII inhibitors in haemophilia A patients. However, as this is a clotting-based assay, the results are affected by emicizumab-kxwh. Therefore, the World Federation of Haemophilia recommend that inhibitor levels in emicizumab-kxwh patients should be identified and monitored via a chromogenic Bethesda assay using bovine reagents (Srivastava *et al.*, 2020). Bovine reagents are necessary to prevent cross reactivity with emicizumab-kxwh. Bethesda assays involving human proteins should be restricted to patients not prescribed this drug (Lippi and Favaloro, 2019). Furthermore, FVIII plasma levels are important for haemophilia A patients and may need to be regularly monitored. When a patient is taking a drug such as emicizumab-kxwh, an APTT-based factor assay cannot be used for plasma FVIII levels and a chromogenic assay is necessary (Krumb *et al.*, 2021).

There are suggestions that there is little need to monitor patients using emicizumab-kxwh by laboratory testing. However, there are concerns that there are risks of procoagulant activity in patients using this drug, who have a breakthrough bleed and are then prescribed other procoagulants, such as activated prothrombin complex concentrate (aPCC) (Hartmann *et al.*, 2018). In the HAVEN 1 trial, two patients experienced thrombotic microangiopathy (TMA) when treated with >100 U/kg of aPCC daily for more than one day after experiencing a breakthrough bleed while using emicizumab-kxwh (Oldenburg *et al.*, 2017). This is because aPCC increases the availability of FIX and FX, resulting in increased thrombin generation and exaggerated procoagulant activity (Hartmann *et al.*, 2018). These findings suggest that there should potentially be a standardised monitoring system in place for patients using emicizumab-kxwh in the event of a breakthrough bleed.

The traditional APTT is not recommended for monitoring of Haemophilia A patients prescribed Emicizumab-kxwh because the drug does not provide a true reflection of the coagulation cascade *in vivo*, as emicizumab-kxwh does not require activation by other coagulation factors (Adamkewicz *et al*., 2020). Most clinical trials involving emicizumabkxwh employed an ELISA assay to monitor plasma Emicizumab-kxwh levels (Adamkewicz *et al*., 2020). However, this is a complex assay that would not be suitable for routine clinical laboratory use

(Kitazawa *et al.*, 2017). With the clear demand for a reliable clinical assay for the measurement of emicizumab-kxwh activity, a modified APTT-based FVIII one step assay (OSA) has been developed (Calhoon *et al.,* 2018, as cited by Müller *et al.*, 2019). This assay has been calibrated against emicizumab-kxwh and has a higher patient dilution than the traditional APTT-based FVIII assay (allowing a larger range of emicizumab-kxwh monitoring). Other than this modification, the assay follows the same principle as the traditional APTT-based FVIII assay and has been in use commercially in Austria, Germany, and Switzerland. The World Haemophilia Federation recommend the use of this assay for the monitoring of emicizumab-kxwh in patients when necessary (Srivastava *et al.*, 2020). Adamkewicz *et al*., 2020, found that this OSA displayed similar emicizumab-kxwh plasma levels when compared to the complicated and non-commercial ELISA assay employed in the HAVEN clinical trials.

The above demonstrates that there is a possible mechanism of routinely measuring emicizumab-kxwh activity and patient FVIII plasma levels. However, obstacles may remain for the analysis of other coagulation factors measured by the APTT assay (FIX, FXII and FXIII).

BENEFITS OF EMICIZUMAB-KXWH FOR HAEMOPHILIA A PATIENTS

Clinical trials to date illustrate the value of emicizumab-kxwh for haemophilia A patients. This drug has revolutionised treatment, despite experts expecting gene therapy to be the next step for haemophilia A (Morfini and Marchesini, 2020). While FVIII concentrates still offer a substantial prophylactic option, emicizumab-kxwh has demonstrated itself as far superior with many advantages, primarily the decreased ABR associated with it.

While analysis of the ABR is vital for understanding the efficacy of emicizumab-kxwh, the quality of life for the patient is also an important factor to consider. The HAVEN 1 study conducted by Oldenburg *et al.*, 2017, used numerical values to assess the quality of life as reported by the participants in the trial, with the lower scores indicating a better quality of life. Those receiving 1.5 mg/kg of emicizumab-kxwh per week had a score of 30.19, while those receiving no treatment had a score of 57.14 (). Scores were calculated based on answers given by patients in a questionnaire given to haemophilia A patients prescribed emicizumab-kxwh.

Self-administration of emicizumab-kxwh is hugely advantageous for haemophilia A patients as it avoids intravenous administration by a healthcare professional two to three times per week (Pipe *et al.*, 2019; Srivastava *et al.*, 2020) allowing haemophilia A patients to become competent in their own care. Should it be possible, 84% of all patients admit that they are willing to self-administer their medication leading to increased patient independence, satisfaction, and increased knowledge about their drugs (Vanwesemael *et al.*, 2018). There are several skills required by patients for self-administration of emicizumab-kxwh such as bleed recognition, record keeping of their regimen and self-infusion skills (Srivastava *et al.*, 2020). Self-administration of emicizumab-kxwh also eliminates the need for central venous access devices (CVADs) in paediatric patients which can often become infected, and venous access in adults which can sometimes be difficult (Srivastava *et al.*, 2020). For paediatric patients and patients who require care assistants, self-administration may not be possible. A study conducted by Hoffmann-La Roche, (2021) showed that 100% of care givers preferred emicizumab-kxwh administration over other haemophilia A prophylactic treatments as it allowed a lower treatment frequency and had less of an impact on daily activities.

The main benefit of emicizumab-kxwh can be observed by the report from HAVEN 3 that demonstrates that the ABR decreased by 68% when a haemophilia A patient moved from FVIII concentrates prophylaxis to emicizumab-kxwh prophylaxis (Mahlangu *et al.*, 2018). Even though emicizumab-kxwh is not readily available worldwide, it is thought to be a cost-effective treatment as it decreases hospital visits, morbidity, and mortality for the patients (Srivastava *et al.*, 2020). The decreased ABR in conjunction with self-administration and less hospitalisations and deaths provides clear evidence for patients to move to emicizumab-kxwh therapy when possible. Although thus far, congenital haemophilia A has been the focus of studies, Emicizumab-kxwh has also been reported to be an effective agent to treat acquired haemophilia A (Knoebl *et al.*, 2021).

DISADVANTAGES OF EMICIZUMAB-KXWH

While emicizumab-kxwh offers several advantages as a haemophilia A prophylaxis over other therapies, there are also some concerns associated with the drug that should not be overlooked. Young *et al.*, (2019), reported that nasopharyngitis and site injection reactions were observed in 37.5% and 30.7%, respectively, of paediatric participants in the HAVEN 2 study. However, these were all considered non-serious events and did not require treatment. Other adverse events that have been noted less commonly in patients using emicizumab-kxwh are headaches, arthralgia, upper respiratory tract infections and pain in extremities (Pipe *et al.*, 2019).

One of the more serious complications that have been observed in patients using emicizumabkxwh is thrombotic microangiopathy (TMA). This complication has been observed in two patients using 1.5 mg/kg per week emicizumab-kxwh who experienced a breakthrough bleed and were treated with aPCC (Oldenburg *et al.*, 2017). Therefore, it is recommended that patients who experience breakthrough bleeding are treated with episodic recombinant FVII (rFVII) or other bypassing agents. However, should aPCC be the only bypassing agent available, the lowest dose expected to achieve haemostasis should be administered (Young *et al.*, 2019).

A dilemma currently faced by many clinicians prescribing patients with emicizumab-kxwh is the efficacy of the drug over time and the development of ADAs with neutralising potential. ADAs have been reported in clinical trials, with two participant showing neutralising potential causing emicizumab-kxwh to have a loss of efficacy (Young *et al.*, 2019). This may be a cause for concern as more patients begin to use the drug and long-term data is unavailable. Additionally, should patients develop ADAs after using emicizumab-kxwh for some time, a change of therapy may be required. As 20% of patients develop inhibitors to FVIII concentrates (Walsh *et al*., 2015) and there are concerns that older / adult patients using FVIII concentrates for the first time may have a large immune response to the drug there are suggestions that age should be aforethought when considering a switch of therapies at a later age (Krishna and Nadler, 2016). Perhaps this could be overcome by administering low doses of FVIII concentrates infrequently in conjunction with emicizumab-kxwh.

While emicizumab-kxwh offers many advantages to haemophilia A patients, it is not available in many parts of the world and several countries still rely on fresh frozen plasma (FFP). Developed countries have moved away from the use of FFP due to the risks associated with bacterial and viral pathogens being present (Srivastava *et al.*, 2020). Therefore, treatment options for patients often rely on the cost and availability of therapies.

CONCLUSIONS

Despite the prospect that gene therapy could have revolutionised haemophilia A therapy, unexpectedly emicizumab-kxwh, a bi-specific antibody, has done just that. This therapy offers a convenient and highly effective alternative to FVIII concentrates that have been the standard approach to therapy for several years. Furthermore, emicizumab-kxwh may be the only effective therapy available for bleeding control for some haemophilia A patients with high titres of FVIII inhibitors. However, this is not to suggest that gene therapy will not offer a permanent treatment option in the future.

Suggestions have been made that emicizumab-kxwh should be administered as it demonstrates superiority to FVIII concentrates and offers several advantages to haemophilia A patients (Le Quellec and Negrier, 2018; Oldenburg *et al.*, 2017). It is now the recommended treatment by the World Haemophilia Federation for patients who possess a FVIII inhibitor and are at risk of haemorrhage (Srivastava *et al.*, 2020). However, as there is an increase in the administration of this drug, there may need to be a standardised approach to laboratory testing considered.

The future regarding therapies for haemophilia A is optimistic since the approval of emicizumab-kxwh for routine use. Current and future trials include the investigation of emicizumab-kxwh during minor surgical procedures and the investigation of the efficacy of emicizumab-kxwh in moderate and severe haemophilia A patients playing sports. This may provide evidence that haemophilia A patients, even those with the severe form, could be empowered to live a relatively normal life without too much concern for bleeding events.

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