EHC
european haemophilia consortium

Novel treatments in haemophilia and other bleeding disorders: A periodic EHC Review

2019 Issue Two

Inhibitors Only

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FOREWORD

Welcome to the third edition of the European Haemophilia Consortium's (EHC) periodic review of novel treatments in haemophilia and other bleeding disorders.

This review is meant to provide an overview in the haemophilia therapeutic landscape from January to September 2019. Therefore this issue will solely offer quick snapshots of notable advances in existing clinical trials, initiation of new clinical trials and development of novel molecules/treatments in the area of rare bleeding disorders.

The purpose of this newsletter is to provide up-to-date information to EHC National Member Organisations (NMOs) and to provide their members with a general overview and understanding of a rapidly-evolving landscape of medicinal product developments in rare bleeding disorders. The EHC encourages its NMOs to use and adapt this newsletter to their national needs but takes no responsibility for any changes.

This newsletter provides information by specific type of disorder: haemophilia A and B; inhibitors in haemophilia, and other rare bleeding disorders. The next newsletter will be issued in early 2020.

This edition heavily draws from the information presented at the last Congress of the International Society of Thrombosis and Haemostasis (ISTH).

The EHC wishes to thank its New Products Working Group, which has overseen the content and production of this newsletter. Its members include:

- Dr. Mariëtte Driessens, EHC volunteer,
- Dr. Radoslaw Kaczmarek, EHC Steering Committee member,
- Dr. Dan Hart, EHC Medical and Scientific Advisory Group (MASAG) member,
- Prof. Mike Makris, EHC Medical Advisory Group (MAG) member,
- Mr. Declan Noone, EHC PARTNERS Consultant,
- Asst. Prof. Brian O'Mahony, EHC President,
- Mr. David Page, EHC volunteer,
- Prof. Flora Peyvandi, EHC Medical Advisory Group (MAG) member,
- Dr. Geneviève Piétu, EHC volunteer ,
- Ms. Laura Savini, EHC Public Policy Officer,
- Dr. Uwe Schlenkrich, EHC volunteer, and
- Ilmar Kruis, EHC volunteer.

The EHC also wishes to thank Dr Yvonne Brennan, University of Sydney, for her contribution towards this issue.

The EHC welcomes all treatment developments that may benefit patients in the future. The EHC takes no position on any product type or class reported in this newsletter. This document does not intend to replace the medical advice provided by healthcare professionals.

We hope that the information contained herein is useful and are available for any questions.

Sincere regards,

Brian O'Mahony
EHC President

Amanda Bok
EHC CEO

ABBREVIATIONS

ABR:	Annualised bleeding rate
ADA:	Anti-drug antibodies
AE:	Adverse events
ALT:	Alanine aminotransferase
BPA:	Bypassing agents
CT:	Clinical trial
ED:	Exposure days
EHL:	Extended half-life
F:	Factor
FDA:	Food and Drug Administration
FIX:	Factor IX
FVIII:	Factor VIII
gc:	genome copies
GT:	Gene therapy
h:	Human
HA:	Haemophilia A
HB:	Haemophilia B
hrs	Hours
ISTH:	International Society of Thrombosis and Haemostasis
ITI:	Immune tolerance induction
IU:	International units
IV:	Intravenous
kDA:	Kilodalton
LFT:	Liver function test
NHF:	National Hemophilia Foundation
PEG:	Polyethylene glycol
PWH:	People with haemophilia
r:	recombinant
SAE:	Serious adverse events
SHL:	Standard half-life
SQ:	Subcutaneous
TGA:	Therapeutic Goods Administration
UK:	United Kingdom
US:	United States
vg/kg:	vector genomes per kilogram
VWD:	von Willebrand disease
VWF:	von Willebrand factor
wk:	week
vs:	versus

AN UPDATE ON NOVEL THERAPIES FOR INHIBITOR TREATMENT

By-Passing Agents Therapies

An update on MarzAA

Catalyst Biosciences updated their phase II trial of its SQ factor VIIa (FVIIa) **variant marzeptacog alfa (activated) (MarzAA)** for prophylaxis. In the daily SQ administration for 50 days of MarzAA in nine patients, there was a reduction in the pre-study ABR from 19.8 to 1.6 during treatment. Additionally, the proportion of days with bleeding (PDB), was significantly reduced from a six-month pre-treatment mean of 12.3% to 0.8% during treatment ($p<0.01$). The median ABR and PDB were both reduced to zero during treatment, with seven of nine patients experiencing no bleeds, either traumatic or spontaneous, at their final dose level. There were no anti-drug antibodies or inhibitors to MarzAA detected after administration of a total of 517 SQ doses. SQ administration prolonged the half-life of MarzAA to 16.6 hours, so that trough levels of MarzAA before the next SQ dose were sufficient to provide bleed prevention. MarzAA has been granted orphan drug designation by the US FDA and the EMA for routine prophylaxis to prevent bleeding episodes in individuals with haemophilia A or B with inhibitors.

Non-replacement therapies

Hemlibra® (emicizumab)

There were several updates on the use of **Hemlibra®** presented at the 2019 Congress of the International Society of Thrombosis and Haemostasis (ISTH).

Data pooled from HAVEN 1-4 clinical trials

In one update given during the ISTH Congress, authors pooled data from all clinical trials (CT) *for* ***emicizumab*** in patients with and without inhibitors (0C60.2). This efficacy analysis included data from 400 participants from *CTs HAVEN 1, 2, 3, and 4.* The median usage was 82.4 weeks. Seventy-seven per cent of participants were treated for ≥74 weeks. Authors used a methodology that created a model to estimate the annualised treated bleed rate. The annualised treated bleeding rate (AtBR) rate was calculated to be 1.5 (95% C.I 1.20-1.84). More important, however, is the increasing use of these types of models to look at ABR. This approach is being used as the mean bleeding rate over each subsequent 24-week period decreased. Using this approach will indicate the added benefits of avoiding even one or two bleeding episodes within three months and the potential downstream effects for further bleeding and potentially some sub-clinical bleeds damaging the joint. Across the studies, those with no treated joint bleeds were over 87% after 25 weeks. Over 92% did not report a spontaneous bleeds after 25 weeks. Authors of this poster include representatives from the pharmaceutical industry.

Data on surgical procedures

During the ISTH Congress, there was a report on surgical procedures (214 minor and 19 major surgeries, performed in 113 and 19 patients respectively) from the clinical trials *Haven 1-4* with patients with or without inhibitors using **Hemlibra®**. The majority of minor surgeries (n=141; 65.9%) such as dental and central venous access device (CVAD) procedures were managed without the use of prophylactic factor concentrate. There was no reported information on the use of tranexamic acid and it is unclear if this was used, in particular, for dental procedures. Of these, 128 (90.8%) did not result in treated postoperative bleeds. Of the 19 major surgeries, 16 (84.2%) were managed with prophylactic coagulation factor. Only one of these resulted in a treated postoperative bleed.

Emiczumab monitoring and ADA issue

The increase in the use of **emicizumab** means that clinicians, patients and regulators need to be increasingly cautious about monitoring coagulation factor levels in preparation of surgery and in case of trauma. This information will also be needed in case of using additional treatment products as well as monitoring for adherence issues. Another issue that will need to be tackled is the monitoring of anti-drug antibodies (ADA), which are currently reported as low (5% incidence rate). Clinicians and regulators will need to work towards getting a better understanding of ADA prevalence and their potential impact on efficacy. Finally, a company-independent assay must be developed.
To this end, there is reporting of several laboratories in France (PB0323) developing methods to characterize the performance of, and study the correlation with, FVIII chromogenic assays to assess emicizumab activity. So far, the performance of the FVIII chromogenic assay is showing good precision and reproducibility, and this will be useful in case of clinical suspicion of ADA or poor compliance. Similar approaches for the detection of ADA are also being examined in several other European centres.

Additional data from original bi-specific antibody clinical trial cohort

In another related abstract (PB1416) presented at the Congress, data on bleeding symptoms and daily life were collected from seven patients Haemophlia A with inhibitors. These patients were on prophylaxis using **emicizumab** and belonged to the original cohort of the phase I/II trial in Japan. The median observation period for these patients was 3.6 years. Bleeding rates had reduced in all patients. These patients' joints were affected by chronic historic bleeds, which caused pain, joint swelling, limited mobility and range of motion. The treatment only led to slight improvement or unchanged status concerning joint health. However, patients reported an increase in daily activities and an overall decrease in anxiety.

Safety and tolerability of prophylactic emicizumab in people with inhibitors

Victor Jiménez-Yuste presented interim data (OC60.3) on the safety and tolerability of prophylactic **Hemlibra®** in people with haemophilia A (PwHA) with FVIII inhibitors (*STASEY*) trial. The trial looked at 88 patients, median age 28 (12-80), receiving emicizumab every week for a median duration of 39.2 (range 4.4-57.1) weeks. Authors calculated the mean ABR using a statistical model, and it resulted in 0.5 ABR for treated patients, 1.4 ABR for all patients, 0.2 ABR spontaneous bleeds, 0.3 ABR joint bleeds and very low target joint bleeds. Seventy-one patients had zero treated bleeds (80.7%). Of 17 patients who received treatment for a spontaneous or traumatic bleed, 16 received rFVIIa, and one received FVIII. Eighteen (20.5%) patients reported an emicizumab-related AE, of which injection-site conditions were the most common.

ITI while on Hemlibra®

Within the haemophilia community, there have been many discussions on the need to continue to tolerise FVIII pateints with inhibitors, even when managed with **emicizumab**, as treatment with emicizumab may only defer development of inhbitors rather than prevent them. Therefore, it was interesting to see some data on this topic presented during the ISTH Congress.

The use of a low-dose immune tolerance induction (ITI) regimen with a long-acting rFVIII was described in three case studies from Japan (PB0236). In two cases, the doses, as well as the dosing interval of **Eloctate®/Elocta®**, decreased after starting the patients on **Hemlibra®**. The inhibitor titers decreased in all three cases, and there were no AE observed. The authors suggest that the use of low-dose (less than 50IU/kg) EHL products and twice-weekly ITI under emicizumab, may be an option for the future. It has been suggested that this treatment could be called the Tokyo protocol.

Although the patient cohort is very small, it is useful to consider the concept of tolerising the inhibitor for better bleeding control in the event of bleeding and surgical procedures using lower doses of FVIII.

Carmen Escuriola Ettingshausen also introduced the investigator-initiated *MOTIVATE study* (PB1406), which will investigate the efficacy and safety of “standard of care” ITI vs novel approaches combining FVIII (**Nuwiq®**) and emicizumab, or emicizumab prophylaxis alone, in people with inhibitors.

Fitusiran

An update on fitusiran

Prof. John Pasi presented an update at the ISTH Congress on *Sanofi's* **fitusiran** phase II study for patients *with* haemophilia A or B with or without inhibitors from the most recent data cut in May 2019. This study administers fitusiran once-monthly, subcutaneously (SQ) and aims to improve thrombin generation (TG) by rebalancing haemostasis. The dataset evaluated 34 enrolled patients (haemophilia A (HA) n=27; haemophilia B (HB) n=7; inhibitors, n=14), followed for up to three years, with a median exposure of approximately 23 months. Of the 33 patients examined, the overall median ABR was of 1.08, without the development of antibodies to fitusiran.
To compare pre-study ABR, authors examined 19 patients without inhibitors. Those patients who were previously on either on-demand or prophylaxis reported an ABR of 12 or 2 respectively; reduced to a mean ABR of 1.08. In the inhibitor cohort (n=14), the pre-study ABR was 42 reducing to a median ABR of 1.04. Fourteen patients (all anti-HCV antibody positive) reported increases in alanine aminotransferase (ALT) tests >3 times the upper limit of normal. All were asymptomatic and resolving, with no elevations of bilirubin twice the upper limit of normal.

In a poster presented during the ISTH Congress, authors presented data (PB0324) on the bleed management guidelines developed to mitigate the risk of thrombosis during breakthrough bleeds treated with either replacement factors or bypassing agents (BPA). The guidelines provide information on maximum dosing and frequency of repeated dosing. At the time of ISTH with these revised treatment guidelines, there had been no related thrombotic events as of the data cutoff. The treatment guideline recommends avoiding antifibrinolytics in conjunction with either factor replacement or BPA.

Subsequently, , there was a report of a thrombotic event in the Phase II open label extension trial in a patient with inhibitors. The event has been reported to regulators.

Update on Pfizer's anti-TFPI (marstacimab)

During the ISTH Congress, there was an update (OC11.2) on the data from *Pfizer's* phase I/II clinical trial using a subcutaneous (SQ) anti-tissue factor pathway inhibitor (TFPI) monoclonal antibody **marstacimab (PF-06741086)**. The trial enrolled 26 patients with severe (FVIII or FIX ≤1%) HA or haemophilia B (HB) with or without inhibitors. All received on-demand treatment and had ≥6 bleeding episodes in the six months before starting the trial.
Patients were assigned to one of four cohorts:

- Cohort 1 received 300mg SQ once weekly;
- Cohort 2 received a 300mg SQ loading dose and then 150 mg SQ weekly;
- Cohort 3 received 450mg SQ weekly; and
- Cohort 4 of inhibitor patients received 300mg SQ weekly.

A model-based ABR was used to compare to historic controls. The mean ABR was 27.6 for all patients pre-treatment. Authors reported a decrease across all patient groups after treatment. In the non-inhibitor cohort, mean ABR decreased to between 1.5-4.2. In the inhibitor cohort, the mean ABR decreased to 0.7. This reduction equals a decrease of mean ABR of 85-95% in the non-inhibitor group and 98% in the inhibitor group.

No thrombotic events occurred. Three patients discontinued the trial because of adverse events (AEs). The most common treatment-related AEs were reactions at the injection site. Three patients had anti-drug antibodies (ADA), with no impact on either safety or efficacy.

Concizumab

An update on concizumab in patients with inhibitors

In a late-breaking session at the ISTH Congress[1], authors presented phase I/II clinical trials data for the use of **concizumab** in HA and HB patients with inhibitors (*explorer 4*).

The trial examines a once-daily subcutaneous treatment that inhibits tissue factor pathway inhibitor (TFPI). This clinical trial enrolled 16 HA patients and 10 HB adults, all with inhibitors. Patients in Explorer 4 were randomised 2:1 to either prophylaxis with concizumab or on-demand treatment with recombinant activated factor VII [rFVIIa]. Initial data suggests mean ABR for all bleeds declined from 20.4 to 4.5 bleeds, spontaneous bleeds declined from 18.5 to 2.5, and joint bleeds declined from 15 to 3.2. Optimised dose and trial design were identified, and concizumab is being developed for phase III pivotal trials. Some patients showed anti-concizumab antibodies, but these were transient and did not appear to have any effect on clinical outcomes. Most patients also reached a normal level of thrombin generation, but there were no thromboembolic events, and no significant safety concerns emerged during the study.

Update on SerpinPC from Apcintex

SerpinPC by *Apcintex* targets the anticoagulant enzyme of activated Protein C (aPC), in its approach to rebalancing the coagulation system. The company is due to start phase I/II trials (NCT04073498) at the end of October 2019 for healthy volunteers and March 2020 for patients with haemophilia. The study will be split into three parts: Part 1a will be conducted in healthy male volunteers in the UK (up to 15) and Parts 1b and 2 will be conducted in haemophilia A & B patients in Moldova and Georgia. Part 1a will look at safety and pharmacokinetics is when given as a single dose to healthy volunteers at different strengths and via two different routes of administration (via IV and SQ), with a reduction in ABR being an exploratory endpoint. Part 2 will be a once monthy SQ treatment for 6 months in 20-25 patients.

Other developments in non-replacement therapies

Korea GreenCross has administered the first dose of **MG1113,** an anti-TFPI, to a patient participating in a phase I clinical trial for the drug. The company plans to evaluate the safety of MG1113 in 49 healthy adult and haemophilia patients.

Bayer's escalating dose study of **BAY1093884,** another anti-TFPI, has currently stopped recruiting for its clinical trial (NCT03597022).

Sigilon presented preclinical data demonstrating the feasibility of cellular therapies for bleeding disorders developed with the company's *Shielded Living Therapeutics™* platform. The **SIG-001** implants - small spheres containing engineered human cells optimized for human (h)FVIII, hFIX and hFVII proteins - were placed into the abdomens of wild-type mice. This implant resulted in therapeutic levels of blood clotting factors to treat haemophilia A. The first clinical studies of Sigilon's SIG-001 are expected to begin in the first half of 2020. This may be an interesting possibility for inhibitors for a few reasons. Firstly, they can be implanted, and if there is an issue or a reaction, they can be removed, which may have a distinct advantage in those few patients with anaphylactic inhibitor reactions. Secondly, it may be able to produce a dose respondent, constant supply of rFVIIa and overcome the issues of short half-lives for constant prophylaxis.

[1] Further information on this is also available in abstract LB01.1, available at on ISTH Congress 2019 website.

Takeda conducted some pre-clinical studies to identify **bispecific antibody (bsAbs)** targeting FIXa and FX to increase thrombin generation in the plasma of HA patients. This treatment could potentially provide in the future a differentiated antibody-based therapy for HA with and without inhibitors.

Gene therapy

This review has discussed in the past the theories about gene therapy in patients with inhibitors, and while there is currently a trial that accepts patients with previous inhibitors, there is still a gap for those with current inhibitors. In basic terms, ideas related to gene therapy in inhibitors are that gene therapy would create FVIII proteins (other considerations are important in FIX) and the inhibitor may not recognise it as a foreign protein. If the body does not see the protein as foreign, the continuous production of FVIII protein would eventually lead to immune tolerance and rather than getting a response of increased factor expression in the first few weeks, it might take longer. *UniQure's* **AMT-180** takes a different approach to this problem to hopefully accelerate access for patients with inhibitors without the potential unknown additional risks associated with a current inhibitor. The concept (poster OC 22.3) uses an optimised FIX delivered via AAV vector, which does not require the presence of FVIII to activate FX. This has the benefit of "by-passing" FVIII in the clotting cascade and as a result, is not impacted by FVIII inhibitors. Normally, when bleeding occurs, FIX activates factor X, and FVIII helps in two ways: by changing the shape of FIX, making it far more active, and linking it to FX. AMT-180 uses a modified FIX, that, when activated as a regular FIX would be, is able to activate FX in the absence of FVIII because it already has the shape change. Preclinical studies with FVIII-depleted human plasma with and without inhibitors as well as studies in haemophilia A mice have demonstrated up to 29% of factor VIII-independent mimetic activity.

Company news

Roche and *Spark Therapeutics* announced entering into a definitive merger agreement so that Roche can fully acquire Spark Therapeutics. The merger, initially due to take place in Q2/2019, has been pushed back to provide the U.S. government additional time to complete its review of the proposed transaction