

# Treatment of bleeding episodes in haemophilia A complicated by a factor VIII inhibitor in patients receiving Emicizumab. Interim guidance from UKHCDO Inhibitor Working Party and Executive Committee

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Emicizumab is a bispecific antibody that activates FX to FXa in the absence of FVIII. It has been shown to reduce bleeding episodes in people with haemophilia A complicated by a FVIII inhibitor. Despite the protection against bleeds, some breakthrough bleeds are inevitable and these may require additional haemostatic treatment. Emicizumab has been associated with severe adverse events when co-administered with activated prothrombin complex concentrate. To minimize the risk of adverse events, the UK Haemophilia Centre Doctors' Organisation issues the following updated interim guidance to its Inhibitor Guidelines for managing patients receiving Emicizumab based on the limit published information available in February 2018.

## KEYWORDS

activated prothrombin complex concentrate, emicizumab, haemophilia, inhibitor, thrombosis, thrombotic angiopathy

## 1 | BACKGROUND

Emicizumab<sup>®</sup> (Roche, Basel, Switzerland) is a bispecific antibody that binds to factor (F)IX/IXa and FX/FXa and activates FX to FXa in the absence of FVIII.<sup>1</sup> It has been shown to reduce bleeding episodes in people with haemophilia A complicated by a FVIII inhibitor.<sup>2</sup> Despite the reduction in annualized bleed rate, some breakthrough bleeds are inevitable and these may require additional haemostatic treatment.

Co-administration of Emicizumab and activated prothrombin complex concentrate (aPCC, FEIBA<sup>®</sup>, Shire, Dublin, Ireland) has been associated with thrombotic microangiopathy (TMA), venous thrombosis and skin necrosis. These adverse events have been observed when aPCC is used for more than one day and at cumulative doses higher than 100 u/kg/d.<sup>2</sup> The number of reported patients treated with Emicizumab and aPCC at doses lower than 100 u/kg/d is small;

therefore, the risk of adverse events at lower doses of aPCC cannot be assumed to be zero, especially if aPCC is used for more than 24 hours. To date, there have been no TMA or thrombotic adverse events associated with the co-administration of Emicizumab and recombinant FVIIa (rFVIIa, Novoseven<sup>®</sup>, Novo Nordisk, Bagsværd, Denmark) or FVIII concentrates but the number of patients treated for bleeds on Emicizumab remains relatively small and the risk of thrombotic events with these agents cannot be excluded. Based on theoretical considerations, co-administration of FVIII and Emicizumab may be associated with a lower risk of thrombosis than aPCC and rFVIIa<sup>3</sup> but this remains to be confirmed in published clinical studies.

It is plausible that the venous thrombotic events are related to increased thrombin generation associated with the bispecific antibody interacting with coagulation factors in aPCC.<sup>3</sup> One of the venous thrombotic events was associated with consumptive coagulopathy. The mechanism that causes TMA and skin necrosis is unclear.

To minimize the risk of adverse events associated with the use of Emicizumab, the UK Haemophilia Centre Doctors' Organisation issues the following interim update to its current inhibitor guidelines<sup>4</sup> based on the limited published data available in February 2018.<sup>5</sup> These guidelines are a consensus statement and have been written from the perspective of UK treaters and clinicians. Other countries may need to revise this guidance as appropriate to their healthcare system, and interim advice was issued in the USA in Nov 2017.<sup>6</sup> It is recognized that these guidelines may require revision as new data become available.

## 2 | GENERAL ADVICE

In the United Kingdom, Emicizumab should only be prescribed to patients with FVIII inhibitors by Comprehensive Care Haemophilia Centres (CCC) with expertise in treating patients with inhibitors. The CCC should take full responsibility for the ongoing management and monitoring of the Emicizumab. Patients receiving Emicizumab should have 24-hour access to clinicians with expertise in treating haemophilia with an inhibitor for advice on treatment of bleeding episodes.

Bypassing agents should be stopped the day before Emicizumab is started. All aPCC (FEIBA<sup>®</sup>) should be removed from the patient's home and returned to the CCC before Emicizumab is started. An updated patient-held Bleeding Disorder Card should be issued.

Emicizumab interferes with the one-stage FVIII assay and chromogenic FVIII assays using human coagulation factors. Once Emicizumab has been started, a chromogenic FVIII assay using reagents containing bovine coagulation factors must be used to monitor FVIII replacement. The Bethesda assay utilizing a bovine-based FVIII chromogenic assay must be used.<sup>5,6</sup>

Before Emicizumab is started, samples should be taken to measure antihuman and antiporcine FVIII inhibitor titres. All treatment with Emicizumab, bypassing agents and FVIII must be recorded, including treatment given in hospital. In the United Kingdom, this should be through Haemtrack<sup>7</sup> and reported to the National Haemophilia Database (NHD) through routine mechanisms.

Adverse events<sup>4,8</sup> must be reported both to regulators through appropriate channels and, in the United Kingdom, to the NHD adverse event reporting site. Biochemical changes compatible with TMA should also be reported. Data should be collected prospectively on safety and efficacy especially in relation to coprescription to better inform future guidelines. Emicizumab has a long half-life, and the treatment recommendations described in this guidance should be observed for 6 months after stopping the drug.

## 3 | TREATMENT OF BLEEDING EPISODES

Bleeds should not be treated with aPCC unless no other alternative is available. In patients receiving Emicizumab, for less severe mucosal bleeds, tranexamic acid alone may be sufficient. Tranexamic

### Summary recommendations

Emicizumab should only be prescribed by Comprehensive Care Haemophilia Centres (CCC). Patients should have 24-hour access to clinicians with expertise in treating haemophilia with an inhibitor.

All treatment with Emicizumab, rFVIIa, aPCC and FVIII must be recorded, in the United Kingdom, this would be on Haemtrack, with safety and efficacy data collected prospectively.

Bypassing agents should be stopped 24 hours before Emicizumab is started, and all home supplies of aPCC should be withdrawn.

An antihuman and antiporcine FVIII inhibitor titre should be measured before Emicizumab is started.

First line treatment of bleeds should be rFVIIa. Human FVIII or recombinant porcine FVIII may be options if the bleed does not resolve with rFVIIa and the human or porcine inhibitor titres are low.

Bleeding episodes should not be treated with aPCC unless no other option is available. If used, the initial dose of aPCC should not exceed 50 u/kg.

If a second dose of aPCC is required, the patient should be admitted to hospital for surveillance for the TMA.

Clinical haemostasis during surgery in patients receiving Emicizumab is unpredictable and data are very limited. Non-urgent, major surgery should be deferred until more data are available.

Due to the long half-life of Emicizumab, these treatment recommendations should be followed for 6 months after the drug has been stopped.

Once Emicizumab has been started a chromogenic assay using reagents containing bovine coagulation factors must be used to monitor FVIII replacement. The Bethesda assay utilizing a bovine reagent-based FVIII chromogenic assay must be used.

acid should not be used in conjunction with aPCC but can be used with rFVIIa.

Treatment with additional haemostatic therapy should only be started if a bleed has definitely occurred or after a significant mechanism of injury. In patients receiving Emicizumab, minor bleeds may resolve without additional haemostatic therapy. If the symptoms of a bleed are minor or equivocal, then advice should be sought from the CCC before starting treatment. In some cases, assessment of the symptoms and signs may be needed before deciding whether to initiate additional haemostatic therapy. Definite or severe bleeds should continue to be treated as soon as possible and advice sought from the CCC.

First line treatment of bleeds that require haemostatic replacement therapy should be with rFVIIa, and patients should be closely observed for symptoms of venous and arterial thrombosis. To reduce the risk of

thrombosis, the initial dose of rFVIIa should not exceed 90 µg/kg. Both Emicizumab and rFVIIa cause thrombin generation and rFVIIa given at doses of 45 µg/kg 4 hourly may be efficacious for some bleeds. It is acknowledged that these dosing schedules are not based on published evidence and may need to be revised as more data become available. The schedule is a pragmatic balance between risk of adverse events and the need to adequately treat bleeds. If lower doses or frequencies of rFVIIa do not result in an adequate haemostasis response, rFVIIa should be increased to 90 µg/kg 2 hourly before it is assumed to have failed. The total treatment period may be shortened in some cases because Emicizumab is likely to give partial protection against bleed recurrence. Clinicians and patients/parents should agree the exact dose and frequency of rFVIIa that can be used at home and when advice should be sought from the CCC if the bleed does not resolve.

If a bleed does not respond to full dose rFVIIa<sup>9</sup> and the antihuman FVIII inhibitor titre is low, human FVIII can be considered to treat bleeds, although it is recognized that this may lead to an amnestic response and an increased inhibitor titre. A chromogenic assay using reagents containing bovine coagulation factors should be used to ensure that adequate FVIII levels have been achieved because responses to FVIII will be unpredictable in the presence of an inhibitor.

Recombinant porcine factor VIII (rpFVIII, Obizur®, Shire, Dublin, Ireland) is not licensed for treatment of congenital haemophilia A. However, if the porcine inhibitor is low, treatment of bleeding episodes with rpFVIII can be considered if a bleed has not responded to rFVIIa and aPCC cannot be used at doses less than 100 u/kg/d or the patient develops clinical or laboratory signs of TMA or thrombosis whilst receiving aPCC.

If a severe bleed has not responded to rFVIIa and other treatment options are not available, then use of aPCC should be considered. We recommend that all treatment with aPCC should be initiated and controlled by a senior clinician at a CCC. The first dose of aPCC should not exceed 50 u/kg, even for a severe bleed. A dose of 25 u/kg may be efficacious for some bleeds. A second dose of 25-50 u/kg can be considered on day one, if necessary. These dosing schedules are based on consensus and may need to be revised as more data are published.

If further treatment with aPCC is required, the cumulative dose should not usual exceed 100 U/kg/d. If the bleed does not respond to aPCC at doses less than 100 u/kg/d, and no other treatment options are available, then higher doses of aPCC can be considered if the treating clinician decides that the risk of not treating the bleed clearly outweighs the risk of adverse events.

In patients treated with Emicizumab and aPCC, clinicians should have a high level of suspicion for TMA and venous and arterial thrombotic events. If treatment with aPCC is required for more than one dose, the patient should be admitted to hospital and assessed twice a day for laboratory evidence of TMA. This includes FBC to look for a decrease in haemoglobin and/or platelets, blood film for red cell fragmentation, reticulocytes, D-dimer, renal function, LDH and haptoglobin. If laboratory monitoring suggests the development of TMA, aPCC should be stopped.

The reported episode of skin necrosis was observed in an area of skin that had been treated with local ice therapy. Whether this was

causally related or co-incidental is not known; however, clinicians should be cautious about the use of ice therapy in patients receiving concomitant Emicizumab and aPCC.

## 4 | IMMUNE TOLERANCE INDUCTION

There are no data on the use of Emicizumab prophylaxis to prevent bleeding episodes during immune tolerance induction (ITI), and the safety of Emicizumab in this situation is unproven. Emicizumab should only be considered during ITI for patients with significant and frequent breakthrough bleeds. The dose of FVIII should be tailored to avoid high FVIII levels which will occur as FVIII tolerance is approached.

## 5 | SURGERY

Data describing surgery in patients receiving Emicizumab are very limited, and responses are unpredictable. Consideration should be given to delaying non-urgent cases until further data are available, especially for major surgery.

An abstract described 29 surgeries in 22 patients receiving Emicizumab. Of these 29 surgeries, 15 were dental extractions or central venous access devices (CVAD) procedures, 12 were other minor procedures and 2 were major procedures. No bypassing agent cover was given in 19 cases, whilst bypassing agents were used in 10 cases.<sup>10</sup>

Of the 19 surgeries managed without bypassing agents, there were 5 (26%) postoperative bleeds of which 3 followed dental extractions. One of these 5 postoperative bleeds required rFVIIa treatment, this was an arthroscopic orthopaedic procedure including synovectomy and debridement. Of the 10 cases that were treated with a bypassing agent at the time of surgery (9 rFVIIa and one aPCC, doses or frequencies not reported), there were two postoperative bleeds and both required rFVIIa treatment.<sup>10</sup>

A further case report described a hip replacement performed following 100 µg/kg rFVIIa before the procedure and 80 µg/kg 3 hourly following the procedure. Despite this treatment, a thigh haematoma developed on the first postoperative day which required FVIII replacement by continuous infusion. Of note, thrombin generation parameters were in the normal range, whilst the patient was on Emicizumab prophylaxis and in the perioperative period.<sup>11</sup>

For minor surgery, such as CVAD procedures and dental extractions, consideration may be given to undertaking the procedure using tranexamic acid without additional haemostatic cover. There should be close clinical review for bleeding and rFVIIa used to manage surgical related bleeding if necessary. Alternatively, a single dose of rFVIIa, between 45 and 90 µg/kg can be used with further treatment as required. In patients with low titre inhibitors, human or recombinant porcine FVIII are options but clinicians should take into consideration that an amnestic response may occur preventing

subsequent use of these agents and centres will need to be able to monitor FVIII levels with appropriate assays in real time.

Based on very limited data, major orthopaedic procedures are likely to require additional haemostatic replacement therapy although this does not guarantee adequate haemostasis. We suggest delaying non-urgent major surgery until more data are available. There are no data to support the use of thrombin generation or thromboelastography to monitor haemostasis during surgery with Emicizumab.

## 6 | CONCLUSION

Emicizumab has been shown to decrease the number of bleeds and improve the quality of life for patients with haemophilia A and an inhibitor. Severe adverse events have occurred when Emicizumab is used in association with aPCC. This guidance document aims to give advice to minimize the risk of adverse events. It is recognized that as new data emerge, this guidance will need to be updated. UKHCDO has set a review date of no later than January 2019 but recognize that early updates may be necessary.

## DISCLOSURES

PW Collins has acted as a paid consultant for Roche/Chugai, Shire and Novo Nordisk. R Liesner Roche consultancy fee, Bayer support for meeting and consultancy fee, Octapharma support for meeting speaker fee and consultancy fee, Shire consultancy fee, Novo Nordisk consultancy fee and Sobi lecture fee. M Makris has provided consultancy to Novo Nordisk and Shire. He is the project lead for EUHASS which receives partial funding from Novo Nordisk and Shire. K Talks has acted as a paid consultant to Roche and is PI for the phase 3a safety study of Emicizumab (Stasey study). P Chowdary reports grants from CSL Behring, Bayer, Novo Nordisk, Pfizer and SOBI. Personal fees from Bayer, Baxter, Baxalta (Shire), Biogen Idec, CSL Behring, Freeline, Novo Nordisk, Pfizer, Roche and Sobi. E Chalmers has received honoraria from Boehringer Ingelheim, Roche and CSL and an educational grant from CSL. G Hall has no conflicts of interest to declare. A Riddell honorarium for participating in Roche Products Limited Chigai Pharma UK coagulation laboratory advisory board. CL Percy is investigator on Stasey study funded by Roche. CR Hay has been a speaker for Shire, Novo Nordisk and Roche. He has advised Shire, Novo Nordisk and Roche. He has no relevant shareholdings. DP Hart has received speaker fees from Shire and Novo Nordisk and consultancy fees from Roche, Shire and Novo Nordisk.

## AUTHOR CONTRIBUTIONS

PWC wrote the first draft in consultation RL, DPH, PCh and MM. All authors provided critical review and comment.

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