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Collins, P., Liesner, R., Makris, M. orcid.org/0000-0001-7622-7939 et al. (7 more authors) (2018) 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. Haemophilia, 24 (3). pp. 344-347. ISSN 1351-8216

https://doi.org/10.1111/hae.13495

Treatment of bleeding episodes in haemophilia A complicated by a factor VIII inhibitor in patients receiving Emicizumab.

Guidance from UKHCDO Inhibitor Working Party and Executive Committee.

January 10th 2018

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Background

Emicizumab is a bispecific antibody that binds to factor (F)IX/IXa and FX/FXa and 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 (Oldenburg 2017). Despite reduction in annualised 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) has been associated with thrombotic microangiopathy (TMA), venous thrombosis and skin necrosis. These adverse events have been observed when aPCC was used for more than one day and at cumulative doses higher than 100 u/kg/day (Oldenberg 2017). The number of reported patients treated with Emicizumab and aPCC for more than one day at doses *lower* than 100 u/kg/day is small (n=5), 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) or FVIII concentrates but the number of patients treated for bleeds on Emicizumab remains relatively small.

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. One of the venous thrombotic events was associated with consumptive coagulopathy. The mechanism that causes TMA and skin necrosis is unclear.

In order to minimise the risk of adverse events associated with the use of Emicizumab the UK Haemophilia Centre Doctors' Organisation issues the following update to its current inhibitor guidelines (Collins 2013) based on data available in January 2018. It is recognised that these guidelines may require revision as new data become available.

General advice

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) 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 assay using plasma containing bovine coagulation factors must be used to monitor FVIII replacement. The Bethesda assay utilising a bovine-based FVIII chromogenic assay must be used.

Before Emicizumab is started, samples should be taken to measure anti-human and anti-porcine FVIII inhibitor titres.

All treatment with Emicizumab, bypassing agents and FVIII must be recorded on Haemtrack, including treatment given in hospital. Treatment must be reported to the National Haemophilia Database (NHD) through routine mechanisms.

Adverse events (as listed in the MHRA EAMS treatment protocol) must be reported both to regulators through appropriate channels and to the NHD adverse event reporting site. Biochemical changes compatible with TMA should also be reported.

Emicizumab has a long half-life and the treatment recommendations described in this guidance should be observed for 6 months after stopping the drug.

<u>Treatment of bleeding episodes</u>

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 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. 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 required treatment should be rFVIIa. 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. However, if lower doses of rFVIIa do not result in an adequate haemostasis response rFVIIa should be increased to 90 µg/kg 2 hourly before rFVIIa 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 (Astermark 2007) and the anti-human FVIII inhibitor titre is low, human FVIII can be considered to treat bleeds, although it is recognised that this may lead to an amnestic response and an increased inhibitor titre. A chromogenic assay using plasma containing bovine coagulation factors should be used to ensure that adequate FVIII levels have been achieved.

Recombinant porcine factor VIII (rpFVIII, Obizur) 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/day 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.

If further treatment with aPCC is required the cumulative dose should not usual exceed 100 U/kg/day. If the bleed does not respond to aPCC at doses less than 100 u/kg/day, 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, 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.

<u>Immune tolerance induction</u>

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.

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 describes 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 (Kruse-Jarres R 2017).

Of the 19 surgeries managed without bypassing agents there were 5 (26%) post-operatives bleeds of which 3 followed dental extractions. One of these 5 post-operative bleeds required rFVIIa treatment, this was an arthroscopic orthopaedic procedure including synovectomy and debridement.

Of the 10 cases who received a bypassing agent at the time of surgery (9 rFVIIa and one aPCC, doses or frequencies not reported) there were two post-operative bleeds and both required rFVIIa treatment (Kruse-Jarres R 2017).

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 post-operative 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 peri-operative period (Santagostino 2017).

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 45-90 µg/kg can be used with further treatment as required.

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.

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.

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

An anti-human and anti-porcine 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.

All treatment with Emicizumab, rFVIIa, aPCC and FVIII must be recorded on Haemtrack.

Review date: no later than January 2019

References

Astermark J, Donfield SM, DiMichele DM, Gringeri A, Gilbert SA, Waters J and Berntorp E, for the FENOC Study Group. A randomized comparison of bypassing agents in hemophilia complicated by an inhibitor: the FEIBA NovoSeven Comparative (FENOC) Study. Blood 109, 546-551, 2007.

Collins PW, Chalmers E, Hart DP, Liesner R, Rangarajan S, Talks K, Williams M, Hay CR;
UK Haemophilia Centre Doctors Organisation.
Diagnosis and treatment of factor VIII and IX inhibitors in congenital haemophilia: (4th edition).
UK Haemophilia Centre Doctors Organization. Br J Haematol. 2013 160:153-70.

Oldenburg J, Mahlangu JN, Kim B, Schmitt C, Callaghan MU, Young G, Santagostino E, Kruse-Jarres R, Negrier C, Kessler C, Valente N, Asikanius E, Levy GG, Windyga J, Shima M. Emicizumab Prophylaxis in Hemophilia A with Inhibitors. N Engl J Med 377:809-818, 2017.

Kruse-Jarres R, Callaghan MU, Croteau SE, Jimenez-Yuste V, Khoo L, Liesner R, Matsushita T, Recht M, Young G, Chang T, Dhalluin C, Mu Y, Xu J, Devenport J, Ko RH Solari P* and Oldenburg J. Surgical experience in two multicenter, open-label phase 3 studies of Emicizumab in persons with hemophilia A with inhibitors (HAVEN 1 and HAVEN 2). ASH 2017 abstr 89.

Santagostino E, Mancuso M, Novembrino C, Boscolo MA, Clerici M, Pasta G, Solimeno LP, and Peyvandi F. Management of joint replacement in hemophilia a with inhibitors during Emicizumab prophylaxis. ASH 2017 abstr 2360.