

REVIEW ARTICLE

Management of bleeding and invasive procedures in haemophilia A patients with inhibitor treated with emicizumab (Hemlibra[®]): Proposals from the French network on inherited bleeding disorders (MHEMO), the French Reference Centre on Haemophilia, in collaboration with the French Working Group on Perioperative Haemostasis (GIHP)

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Abstract

Introduction: Emicizumab (Hemlibra[®]) recently became available and requires an adaptation for managing bleeding, suspected bleeding and emergency or scheduled invasive procedures in haemophilia A patients with inhibitor. This implicates a multi-disciplinary approach and redaction of recommendations for care that must be regularly adapted to the available data.

Aim: The following text aims to provide a guide for the management of people with haemophilia A with inhibitor treated with emicizumab in case of bleeding or invasives procedures.

Methods: The French network on inherited bleeding disorders (MHEMO), the French Reference Centre on Haemophilia (CRH), in collaboration with the French Working Group on Perioperative Haemostasis (GIHP) have been working together to make proposals for the management of these situations.

Results: Haemostatic treatment and other medications should be given stepwise, according to the severity and location of the bleeding or the risk of bleeding of the procedure as well as the haemostatic response obtained at each step in order to ensure an optimal benefit/risk ratio.

Conclusion: The lack of data means that it is only possible to issue proposals rather than recommendations.

KEYWORDS

bleeding, emergency, emicizumab, haemophilia, inhibitor, invasive procedures, proposals

1 | INTRODUCTION

Emicizumab (Hemlibra[®]; F. Hoffmann-La Roche) has only recently been available and requires an adaptation for managing bleeding, suspected bleeding and emergent or scheduled invasive procedures in haemophilia A patients with inhibitor. This implicates a multidisciplinary approach and reduction of recommendations for care that must be regularly adapted to the available data. The following text aims to provide a guide for the management of people with haemophilia A with inhibitor treated with emicizumab in case of bleeding or invasive procedures.

The methodology for establishing these proposals was as follows. The French network on inherited bleeding disorders (MHEMO), the French Reference Centre on Haemophilia (CRH), in collaboration with the French Working Group on Perioperative Haemostasis (GIHP) have been working together to make proposals for the management of these situations. Three authors representing each group made the proposals. The different groups then read, discussed and modified these proposals. The proposals were based on data from the literature and experiences collected from the patients treated in the French reference centres (MHEMO).

Emicizumab is a bispecific monoclonal antibody that reproduces to some extent the procoagulant activity of FVIII,¹ and reduces spontaneous bleeding in haemophilia A patients with or without inhibitor.^{2,3} Emicizumab is exclusively used for prophylaxis and subsequent protection against bleeding is therefore only partial, with a bleeding risk in treated patients at best equivalent to that of patients with mild haemophilia.^{4,5} Emicizumab is administered weekly by subcutaneous injections at a dose of 1.5 mg/kg after a period of 4 weeks with a weekly loading dose of 3 mg/kg.^{5,6} Its elimination half-life is 30 days. The complete disappearance of drug-related effects can therefore only be achieved in theory after 150 days (5 half-lives).^{7,8}

Except for weight, no dosage adjustment is required, especially no adjustment for age, renal or hepatic function, and the

concentration of the drug is stable once the plateau phase is reached. Few cases of immunization against this drug have been reported; however, the reappearance of bleeding events that had disappeared should raise concerns about the development of an anti-drug antibody (ADA).⁹ Importantly, patients treated with emicizumab most often have normal activated partial thromboplastin time (aPTT) and improved thrombin generation *ex vivo*. The shortening of the aPTT is not dose-dependent, and no formal relationship has been demonstrated between increased thrombin generation on emicizumab and clinical efficacy. The concomitant use of activated prothrombin complex concentrates (aPCC) such as FEIBA[®] (FEIBA NF, Baxalta US Inc, a Takeda company) for controlling breakthrough bleedings in doses exceeding 100 U/kg/24 h with a duration of treatment longer than 24 hours in patients treated with emicizumab has been associated with the development of thrombotic microangiopathies (TMA) and venous thrombotic events.² *In vitro* studies have confirmed a synergistic effect between emicizumab and aPCC.¹⁰ No cases of thrombosis or TMA have been reported in the literature so far following administration of recombinant FVIIa (rFVIIa, eptacog alpha, NovoSeven[®]; Novo Nordisk) in patients receiving emicizumab.¹¹ The use of aPCC must therefore be restricted or cautiously used under close and specific supervision of haemophilia treatment centres in situations without alternatives of equivalent therapeutic efficacy, and in this case only reduced dosages should be prescribed. In order to treat possible bleeding complications, patients treated with emicizumab should not use aPCC at home as a first-line therapy (excepting following specific recommendations from the haemophilia treatment centre), but rFVIIa should be preferred. However, some patients are considered to be non-responsive to rFVIIa or to aPCC (discordant patients), and in these cases, it has been proposed to evaluate the thrombin generation profile obtained *in vitro* and *ex vivo* and the patient's previous clinical response to guide the use of the bypassing therapy.¹² However, there is still not enough data to expand this attitude. Moreover, the apparent procoagulant

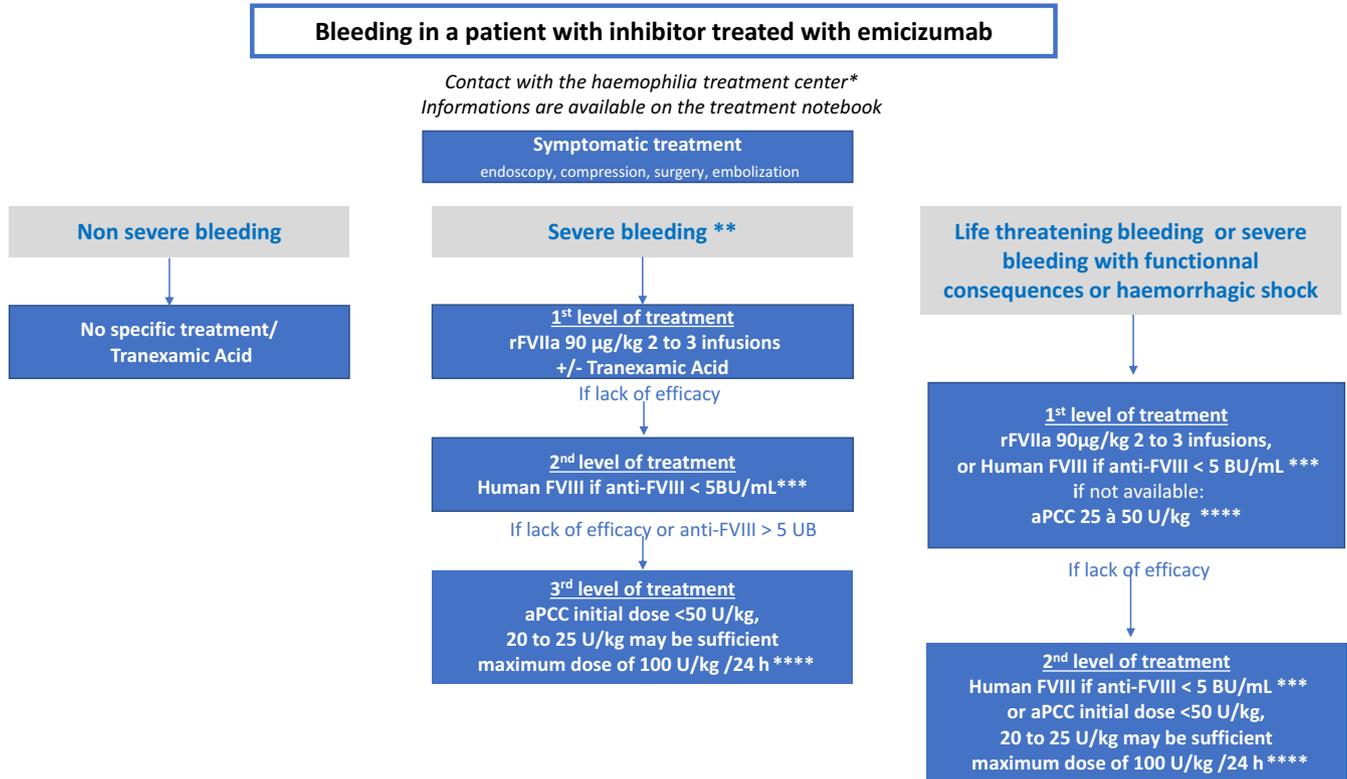


FIGURE 1 Bleeding in a patient treated with emicizumab. *Reference center for rare bleeding disorders. **Bleeding causing a fall in hemoglobin level of 20 g/L or more, or leading to transfusion of two or more units of whole blood or red cells. ***Availability of a recent titer (<1 mo) of inhibitor anti-FVIII <5 BU/mL and between 2-3 h after last rFVIIa infusion. ****Monitoring of platelet count, LDH, renal function, haptoglobin and blood smear with schizocyte testing

activity of emicizumab according to thrombin generation assay may vary substantially according to trigger reagent or phospholipid composition.¹³

Emicizumab-treated haemophilia A patients may develop acute haemorrhagic manifestations, most often traumatic, or require emergency or scheduled surgery or invasive procedures that may necessitate additional haemostatic treatment. Additional injections of emicizumab in these situations are not indicated, and this drug should therefore never be used in an emergency setting.

2 | MANAGEMENT OF A BLEEDING EPISODE

In patients treated with emicizumab facing bleeding, additional haemostatic treatment is not systematically required and depends on the nature and severity of the bleeding episode, the circumstances of the occurrence, the possibility of documenting it by imaging if necessary and the possibility to apply symptomatic treatments for bleeding (endoscopy, compression, surgery, embolization, etc). As the plasma concentration of emicizumab is stable after the first month of treatment and the dosage does not need to be adjusted, the date of the last emicizumab injection does not a priori influence the patient's haemostatic status.

It is recommended as a first step to contact the haemophilia treatment centre in which the patient is being followed. Some informations are available on a rare disease-specific card or in the patient notebook.

Haemostatic treatment and other medications should be given stepwise, according to the severity and location of the bleeding, as well as the haemostatic response obtained at each step in order to ensure an optimal benefit/risk ratio. Thus, three levels of treatment can be proposed (Figure 1).

2.1 | 1st level of treatment

2.1.1 | Tranexamic acid

In case of isolated mucosal bleeding, treatment with tranexamic acid alone at the usual doses (2-4 g/24 h per os or iv divided into three or four doses for adults and 20 mg/kg over 24 hours divided into three or four doses for children from 1 year of age) is proposed.

2.1.2 | rFVIIa

In all cases of severe bleeding, as defined by the ISTH criteria,¹⁴ that is, life-threatening or in a critical organ including joint bleeds and

large muscle haematomas, or bleeding causing a fall in haemoglobin level of 20 g/L or more, or leading to transfusion of two or more units of whole blood or red cells, the first-line drug should be rFVIIa at a dose of 90 µg/kg. However, some authors have proposed lower doses such as 45 µg/kg, that could theoretically be as effective, but there is still limited data available supporting this lower dosage. Tranexamic acid can be combined with rFVIIa. The first injection of rFVIIa can be made at home after medical advice from the haemophilia treatment centre, possibly in conjunction with the emergency medical team intervening at home. If repetitive injections are likely to be required considering the medical condition, hospital admission is required. Frequency of injections and duration of rFVIIa treatment should be adapted to the severity of the medical condition. Spacing of injections and/or decreased dosage should be considered as soon as the bleeding situation is controlled.

Noticeably, human FVIII (plasma derived or recombinant FVIII) can also be used if the anti-FVIII inhibitor titre, recently (dosage during the previous month excluding the situation of possible anamnesis due to further FVIII infusions) measured by an appropriate assay (ie a chromogenic Bethesda method using bovine reagents insensitive to emicizumab) is low (<5 BU/mL). If rFVIIa is not available, or if human FVIII cannot be used or is not available, the first-line drug should be aPCC with an initial dose of 20-25 U/kg.

2.2 | 2nd level of treatment

If rFVIIa combined with tranexamic acid is inefficient (persistence of bleeding despite three injections at 2 or 3 hours intervals at a dose of 90 µg/kg), and if the anti-FVIII inhibitor titre is low (<5 BU/mL), infusion of human FVIII concentrate can also be considered within 2-3 hours after the last rFVIIa administration.¹⁵ This underlines that inhibitor titration, which is not performed in all centres, should be part of the routine follow-up of patients with inhibitors treated with emicizumab. How the presence of both emicizumab and FVIII affect haemostasis in patients with Haemophilia A remains poorly known? However, given the respective efficacy of emicizumab and FVIII to stimulate FIXa activity,⁴ it can be hypothesized that injected FVIII has the same efficacy in the presence or absence of emicizumab.

In the case of a severe bleeding, the dose of FVIII required should be calculated on the basis of the inhibitor titre (<5 BU/mL) and in order to maintain FVIII above 80 IU/dL at least during the first 48 hours. To maintain this target, it may be sometimes required to increase the frequency of bolus injections, and even to switch to continuous infusion.¹⁵ Plasma FVIII concentrations should be monitored using a chromogenic assay method using bovine reagents (no interference with the presence of emicizumab). FVIII measurements by a chronometric method (or any other chronometric test based on clotting activity) or by a chromogenic method using reagents of human origin are not appropriate in patients treated with Hemlibra.

Recombinant porcine FVIII (Obizur[®], susoctocog alpha, Baxalta US Inc, a Takeda company) is not yet approved in this indication;

however, the use of this drug could be considered in case of severe bleeding not responding to bypassing agents if the titre of porcine anti-FVIII inhibitor is low.

2.3 | 3rd level of treatment

In case of lack of efficacy of rFVIIa (persistence of bleeding despite three injections at 2-3 hours intervals at a dose of 90 µg/kg) combined with tranexamic acid, followed by a lack of efficacy of human FVIII, or in case of lack of efficacy of rFVIIa with a high anti-FVIII inhibitor titre (≥5 BU/mL), aPCC can be prescribed under strict medical guidance.

The first dose of aPCC should not exceed 50 U/kg, and an initial dose of 20-25 U/kg may be sufficient to control the bleeding. In case of inefficacy, a second dose of aPCC may be proposed 12 hours later, taking care to never exceed a maximum dose of 100 U/kg over 24 hours. Given the synergistic action between aPCC and emicizumab, the dose of aPCC must always be lower than that used in haemophilia A with inhibitor without emicizumab prophylaxis.

As mentioned previously, it has been suggested that the efficacy and safety of combination of emicizumab and aPCC could be monitored using thrombin generation assay. However, in this specific situation of bleeding episode there are still no data to support this proposal.

Monitoring of platelet count, LDH, renal function, haptoglobin and blood smear with schizocyte testing is then essential to detect thrombotic microangiopathy signals.

3 | MANAGEMENT OF URGENT OR PLANNED SURGERY OR INVASIVE PROCEDURE UNDER THE SUPERVISION OF HAEMOPHILIA TREATMENT CENTRES

Given the very long half-life of emicizumab, it is unnecessary and unrealistic to discontinue this treatment before an invasive procedure or surgery. emicizumab, even at very low plasma concentrations, induces a shortening of the aPTT ('normal' or subnormal in most cases) although haemostasis is only partially corrected. Given the prolonged half-life of emicizumab, this effect on aPTT may persist for up to 6 months after the last administration of emicizumab.

To date, and due to a lack of data in this context, neuraxial anaesthesia (epidural and spinal) is generally contraindicated.

3.1 | Surgery with minor bleeding risk

For procedures with a minor bleeding risk such as (non-exhaustive) compressible vascular access (central venous catheter insertion or removal), simple dental avulsion (<3 teeth)/dental care, endoscopies without biopsies, and in the absence of any additional

Urgent or planned surgery or invasive procedure in patients with inhibitor treated with emicizumab

Contact with the haemophilia treatment center
Informations are available on the treatment notebook*

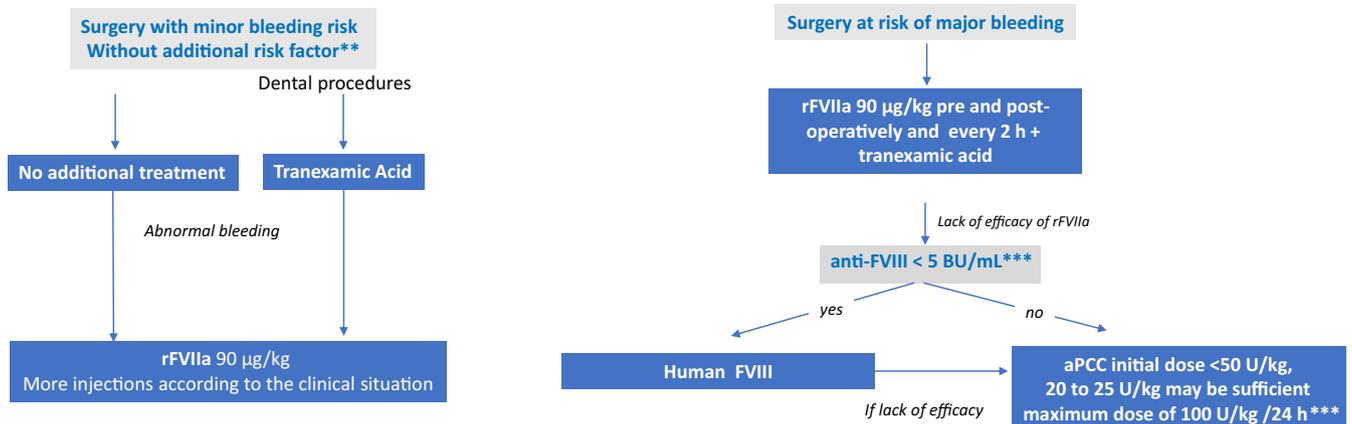


FIGURE 2 Urgent or planned invasive procedure in a patient treated with emicizumab. *Reference center for rare bleeding disorders. **Compressible vascular access (insertion or removal), simple dental avulsion (<3 teeth)/dental care, endoscopies without biopsies. ***Using a chromogenic assay method using a reagent containing bovine coagulation factors. ****Monitoring of platelet count LDH, renal function, haptoglobin and blood smear with schizocyte testing

bleeding risk (eg dental abscess, multiple re-interventions on an implantable chamber site), it is possible not to prescribe additional haemostatic drugs such as rFVIIa. This attitude should be carefully evaluated by the medical team (haematologist, anaesthesiologist and surgeon) depending on the risk related to the procedure planned for the patient.

Tranexamic acid must be systematically prescribed for dental procedures (per os and with mouthwash).

In case of postoperative bleeding considered abnormal, the first-line treatment is rFVIIa at the initial dose of 90 µg/kg to be repeated according to the clinical situation. The frequency and duration of rFVIIa treatment is adapted to the clinical situation. Spacing of injections and/or decreased dosage should be considered as soon as possible (Figure 2).

3.2 | Surgery with major bleeding risk

Any non-minor surgery is considered major.

The three levels of treatment described for bleeding episodes are implemented in this setting and described in Figure 2.

3.2.1 | 1st level of treatment

rFVIIa

The first-line treatment is rFVIIa at a dose of 90 µg/kg administered 15 minutes preoperatively, followed by postoperative injections every 2-3 hours and then gradually spacing the intervals between injections. Tranexamic acid should be associated with rFVIIa.

3.2.2 | 2nd level of treatment

Human FVIII can be used if the inhibitor titre is low at the time of the procedure (<5 BU/mL). It is therefore important to have a recent titration of the inhibitor for surgery, which must be performed using a chromogenic Bethesda method using bovine reagents (insensitive to emicizumab). The dose required should be calculated on the basis of the inhibitor titre, in order to maintain FVIII concentration above 80 IU/dL at least during the first 48 hours for a major surgery.

3.2.3 | 3rd level of treatment

If rFVIIa is ineffective and human FVIII cannot be used or is ineffective, aPCC may be prescribed at a reduced dosage (always <100 U/kg/24 h) under strict clinical and biological surveillance. The first dose should not exceed 50 U/kg, and 20-25 U/kg may be sufficient. Treatment should then be continued, ensuring that it never exceeds 100 U/kg/24 h. Monitoring of platelet count, LDH, renal function, haptoglobin and blood smear with schizocyte testing is then essential (to detect early signs of TMA). In case of failure of this 3rd level of treatment therapy, a multidisciplinary decision should be made without delay regarding potential surgery, embolization and all local haemostatic procedures. Each line of treatment that has been performed should also be carefully checked regarding the dosing and the number of injections administered. Combination of bypassing agents could be an option in case of failure of all other strategies even if the concomitant use of rFVIIa and aPCC is associated with an increased risk of thrombotic complications, even in the absence of emicizumab.¹⁶

TABLE 1 Influence of emicizumab on different haemostasis tests

Affected tests ¹⁸	Unaffected tests
<ul style="list-style-type: none"> • aPTT and all tests based on aPTT (shortening) • Detection and titration of anti-FVIII inhibitors with clot-based assays • One-stage chromometric assay of FVIII • Chromogenic assay of FVIII (and FIX) with human reagents (non-proportional increase) • Fibrinogen level measured with a PT-derived method (overestimation) • Determination of factors IX, XI, XII (non-proportional increase) • Search for lupus anticoagulant • ACT measurement (shortening) 	<ul style="list-style-type: none"> • Fibrinogen level measured with Clauss-derived methods • Prothrombin time • Assays of prothrombin complex factors (FII, V, VII, X) • Chromogenic assay of FVIII with bovine reagents • Detection and titration of anti-FVIII inhibitors by a chromogenic method using bovine reagents • Thrombin time • Anti-Xa activity • Antithrombin level • D Dimers and other immunological assays

Abbreviations: ACT, activated clotting time; aPTT, activated partial thromboplastin time.

4 | CHANGES IN HAEMOSTASIS TESTS IN PATIENTS RECEIVING EMICIZUMAB

Emicizumab does not require activation by thrombin and its effect on the aPTT is more pronounced than that of factor FVIII.^{17,18} aPTT-based FVIII activity and FVIII inhibitor titre measurements are influenced by the presence of emicizumab. Consequently, all conventional aPTT-based clotting assays, including one-stage FVIII assays, should not be performed while on emicizumab, as they yield misleading results (ie artifactually elevated FVIII activity; Table 1).

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AUTHOR CONTRIBUTIONS

SS (GIHP, MHEMO) wrote the manuscript. YG (GIHP, MHEMO) and CN (CRH, MHEMO) supervised the redaction and critically revised the manuscript. AG (GIHP), AH (CRH), HC (CRH, MHEMO), DL (GIHP, MHEMO), AR (MHEMO), SR (GIHP), PF (GIHP), JG (MHEMO), EdM (GIHP), VC (CRH, MHEMO), BW (CRH, MHEMO) and PA (GIHP) contributed to the writing of the manuscript and critically revised the manuscript.

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