



REVIEW ARTICLE

Emicizumab treatment: Impact on coagulation tests and biological monitoring of haemostasis according to clinical situations (BIMHO group proposals)

Christophe Nougier¹ | Emmanuelle Jeanpierre² | Catherine Ternisien³ |
Valérie Proulle⁴ | Nathalie Hezard⁵ | Claire Pouplard⁶ | Dominique Lasne^{7,8} |

With contributions from the Working Group on Biology of Haemorrhagic Disorders (BIMHO), Under the Aegis of GFHT)

¹Laboratoire d'hématologie-hémostase, Centre de Biologie et Pathologie Est, Hospices civils de Lyon, Bron, France

²CHU Lille, Institut d'Hématologie Transfusion, Inserm U1011, Lille, France

³Service d'Hématologie Hémostase, Hôtel-Dieu, CHU de Nantes, France

⁴Service d'Hématologie Biologique, CHU Bicêtre, AP-HP, Université Paris Sud Saclay, INSERM U1176, Le Kremlin-Bicêtre, France

⁵Laboratoire d'hématologie, Hôpitaux de Marseille, Marseille, France

⁶Service d'Hématologie Hémostase, Hôpital Trousseau, CHU de Tours, EA 7501 Université François Rabelais, Tours, France

⁷Laboratoire d'hématologie générale, Hôpital Necker, AP-HP, Paris, France

⁸Université Paris Sud Paris Saclay, Inserm U1176, Le Kremlin-Bicêtre, France

Correspondence

Christophe Nougier, Laboratoire d'hématologie-hémostase, Centre de Biologie et Pathologie Est, Hospices civils de Lyon, Bron 69500, France.
Email: christophe.nougier@chu-lyon.fr

Abstract

Emicizumab, a bispecific humanised monoclonal antibody restoring to some extent the function of activated FVIII deficient in haemophilia A, represents a major therapeutic advance in the management of haemophilia A patients. No dosage adjustment is required, which leads to a major change for patients used to regular biological monitoring which is particularly burdensome in the case of substitution therapy. In some circumstances, such as before an invasive procedure or in case of bleeding, biological monitoring will be necessary and emicizumab's interference with haemostasis tests, particularly those based on an activated partial thromboplastin times (aPTT), must be known to best interpret the tests and to select the most appropriate methods to guide therapy. The normalisation of aPTT in patients treated with emicizumab is not sufficient to consider haemostasis as normalised. In the event of administration of FVIII to a patient receiving emicizumab, the determination of FVIII should use a chromogenic method using non-human reagents. Coagulation global tests have been proposed to evaluate the biological response when using bypassing agents in patients treated with emicizumab, but the usefulness must be confirmed. The French group BIMHO presents proposals for biological monitoring of a patient treated with emicizumab according to clinical situations.

KEYWORDS

coagulation assay, emicizumab, haemophilia

1 | INTRODUCTION

Emicizumab (Hemlibra[®]; Roche Chugai) is a bispecific humanised monoclonal antibody that restores to some extent the function of missing activated FVIII (FVIIIa) in patients with haemophilia A, by binding to activated factor IX (FIXa) and factor X (FX),

thereby allowing activation of FX to FXa, resulting in coagulation. Emicizumab obtained marketing authorisation (MA) in the European Union on 23 February 2018, as prophylaxis for bleeding episodes in patients with haemophilia A having developed an anti-factor VIII inhibitor, with level II clinical added value (ASMR/CAV II)¹ and, since 11 March 2019 has also been authorised for

use in haemophilia A patients without inhibitors (ASMR/CAV IV).² It therefore represents major therapeutic progress. The absence of homology between emicizumab and FVIII rules out any risk of cross reaction with inhibitors directed against FVIII, a major complication of replacement therapy using FVIII concentrates, thus making it a preferential prophylactic treatment for haemophiliacs with inhibitors. Phase III clinical studies in adults and children have shown that a subcutaneous injection once a week, or every 2 or 4 weeks, was significantly more effective in preventing induced or spontaneous bleeding compared with standard therapies (recombinant activated factor VII [rVIIa] or activated prothrombin complex concentrates [aPCC]) in haemophiliacs with inhibitors. In the

same way, emicizumab presented good level of safety and efficacy in haemophiliacs without inhibitors as compared to replacement therapy with FVIII concentrates in haemophiliacs without inhibitors.³⁻⁵ Subcutaneous administration with a single injection per week gives rise to a significant improvement in quality of life in patients for whom prophylaxis previously required intravenous infusion of FVIII concentrates 2-3 times per week.⁶ The emicizumab concentrations measured in the HAVEN clinical studies are stable from week 5 of treatment, between 40 and 80 µg/mL,³ which implies predictable pharmacokinetics in all patients not requiring regular laboratory monitoring. Despite these characteristics of emicizumab, the French BIMHO Working Group (*Biology of*

| Tests | Methods | Impact of emicizumab |
|---|--|---|
| Prothrombin Time, INR | Chronometric assay | Acceptable |
| APTT, KCT (kaolin clotting time), ACT (activated clotting time) | Chronometric assay | Substantial shortening starting from 10 µg/mL emicizumab |
| Fibrinogen | Clauss method | Acceptable |
| | Derived fibrinogen | Acceptable |
| Factors II, V, VII, X | Chronometric assay | Acceptable |
| FVIII | Chronometric assay | Uninterpretable activity |
| | Chromogenic assay (Human recombinant reagents) | Uninterpretable activity |
| | Chromogenic assay (Hybrid or bovine reagents) | Undetectable activity |
| | ELISA | Acceptable |
| FIX, FXI, FXII | Chronometric assay | Overestimation |
| | ELISA | Acceptable |
| Anti-FVIII titre (Bethesda method, Nijmegen method) | Chronometric assay | Underestimation of inhibitor titres, false-negative results |
| | Chromogenic assay (bovine or hybrid reagents) | Acceptable |
| Protein C | Chronometric assay | Underestimation |
| | Chromogenic assay | Acceptable |
| | ELISA | Acceptable |
| Protein S | Chronometric assay | Underestimation |
| | Immunoturbidimetry assay (Free PS antigen) | Acceptable |
| | ELISA | Acceptable |
| Antithrombin | Chromogenic assay | Acceptable |
| | Immunoturbidimetry assay (AT antigen) | Acceptable |
| Lupus anticoagulant | APTT | False-negative results |
| | dRVVT | Acceptable |
| Activated protein C resistance (ratio) | Chronometric assay | Underestimation |
| Von Willebrand Factor | Assay of activity | Acceptable |
| | Antigen assay | Acceptable |
| D-dimers | Immunoturbidimetry assay | Acceptable |

TABLE 1 Interferences of emicizumab on commonly used coagulation tests^{11,13,22,28}



Haemorrhagic Disorders, under the aegis of GFHT: Groupe Français d'étude sur l'Hémostase et la Thrombose) was interested in studying haemostasis in patients treated with emicizumab since there is a risk in rare cases of developing a potentially neutralising antibody to emicizumab^{7,8} which can result in treatment failure. Access to a test reflecting the biological efficacy of emicizumab is therefore desirable in such situations. Furthermore, in cases of bleeding, or procedures entailing a risk of bleeding, it is essential to have access to laboratory tests,⁹ and to know how to interpret these tests in patients receiving emicizumab in these situations.¹⁰ National proposals for laboratory monitoring of patients treated with emicizumab are described according to different clinical situations.

2 | EMICIZUMAB AND COAGULATION TESTS

2.1 | Emicizumab interference with coagulation tests

As demonstrated in the studies on plasma from severe haemophilia A patients and normal plasma spiked with emicizumab different haemostasis tests are affected by the presence of emicizumab, which should be taken into consideration for interpretation (Table 1).¹¹⁻¹³

2.1.1 | Rapid shortening of activated partial thromboplastin time (aPTT)

A substantial shortening in activated partial thromboplastin time (aPTT) is observed from low concentrations of circulating emicizumab regardless of the type of reagent used.¹³ This shortening is dose-dependent up to 10 µg/mL. However, this short aPTT does not mean a normal thrombin generation. Indeed, the thrombin generation which measured in sample spiked with 50 µg/mL of emicizumab corresponds to that measured in a minor haemophilia A patient.¹⁴ The strong impact of emicizumab in reducing aPTT is explained by its mechanism of action. Indeed unlike FVIII, this bispecific humanised monoclonal antibody does not require prior activation by thrombin and is therefore immediately effective. aPTT is thus a highly sensitive test but its normalisation in no way implies effective haemostasis. Furthermore, emicizumab interference will be observed with all tests based on aPTT.

2.1.2 | Assay of FVIII activity: variable results according to the methods

One-stage FVIII assay

As One-stage assay (OSA) of FVIII is based on aPTT, it is influenced by the presence of emicizumab. Paradoxically, in a patient with severe haemophilia A treated with emicizumab, clotting activity

equivalent to that obtained with FVIII levels greater than 1.50 IU/mL is, nevertheless, measured.¹³ However, no validated correlation exists between this coagulant activity (mimicking FVIII) and the patient's haemostatic status. Factor VIII (or rather "pseudo-FVIII") OSA should not therefore be performed in patients receiving emicizumab.

Chromogenic assay of FVIII

FVIII activity (FVIII:C) measurement using chromogenic technique in patients receiving emicizumab differs according to the reagents origins (ie, human or animal). The use of a human recombinant reagent kit (Biophen FVIII®:CR, Sysmex) detects FVIII activity which increases with emicizumab in a concentration-dependent manner. This humanised antibody effectively recognises the FIXa and FX present in these reagents. Moreover in our experience, considerable variability is observed between reagent batches, and the chromogenic method with human reagents does not allow reliable monitoring or assessment of haemostatic status in patients treated with emicizumab.¹⁵ Because no binding between emicizumab and animal clotting factors is effective, no detectable activity exists when combined human/animal reagents (Technochrom FVIII®:CR, containing human FIXa reagent and bovine FX reagents) or only animal reagents (Technoclone; Coamatic factor VIII®, Chromogenix; Berichrom FVIII®, Siemens; Trinichrom®, Stago) are used for chromogenic assay of FVIII.^{16,17} Such a test is, however, very useful if FVIII concentrate replacement therapy is administered in combination with emicizumab, for monitoring treatment with exogenous FVIII. It is also the only method available to determine the titre of an anti-FVIII inhibitor in patients receiving emicizumab.

2.1.3 | One-stage assay of factors IX, XI and XII

Because of the sensitivity of aPTT to emicizumab, there is a risk of an overestimation the FIX, FXI and FXII levels measured using one-stage-based assays.¹¹

2.1.4 | Detection and titration of anti-factor VIII inhibitor: adaptation of the Bethesda method

In certain clinical situations such as invasive surgery/procedures or bleeding,⁹ the choice of treatment for patients with haemophilia A with inhibitor and treated with emicizumab is based on accurate evaluation of inhibitor titre. If titre is less than 5 BU/mL, the inhibitor is potentially neutralised by exogenous FVIII, and treatment with FVIII may be considered. The activity of FVIII administered may thus be assayed using a chromogenic method, with animal-origin reagents. Inhibitor titre must be determined using chromogenic methods insensitive to the presence of emicizumab, and conventional Bethesda or Nijmegen methods, based on one-stage assay of FVIII in the different mixtures (Figure 1), cannot be used. As shown in Figure 2, FVIII levels measured in test mixtures (patient + control)

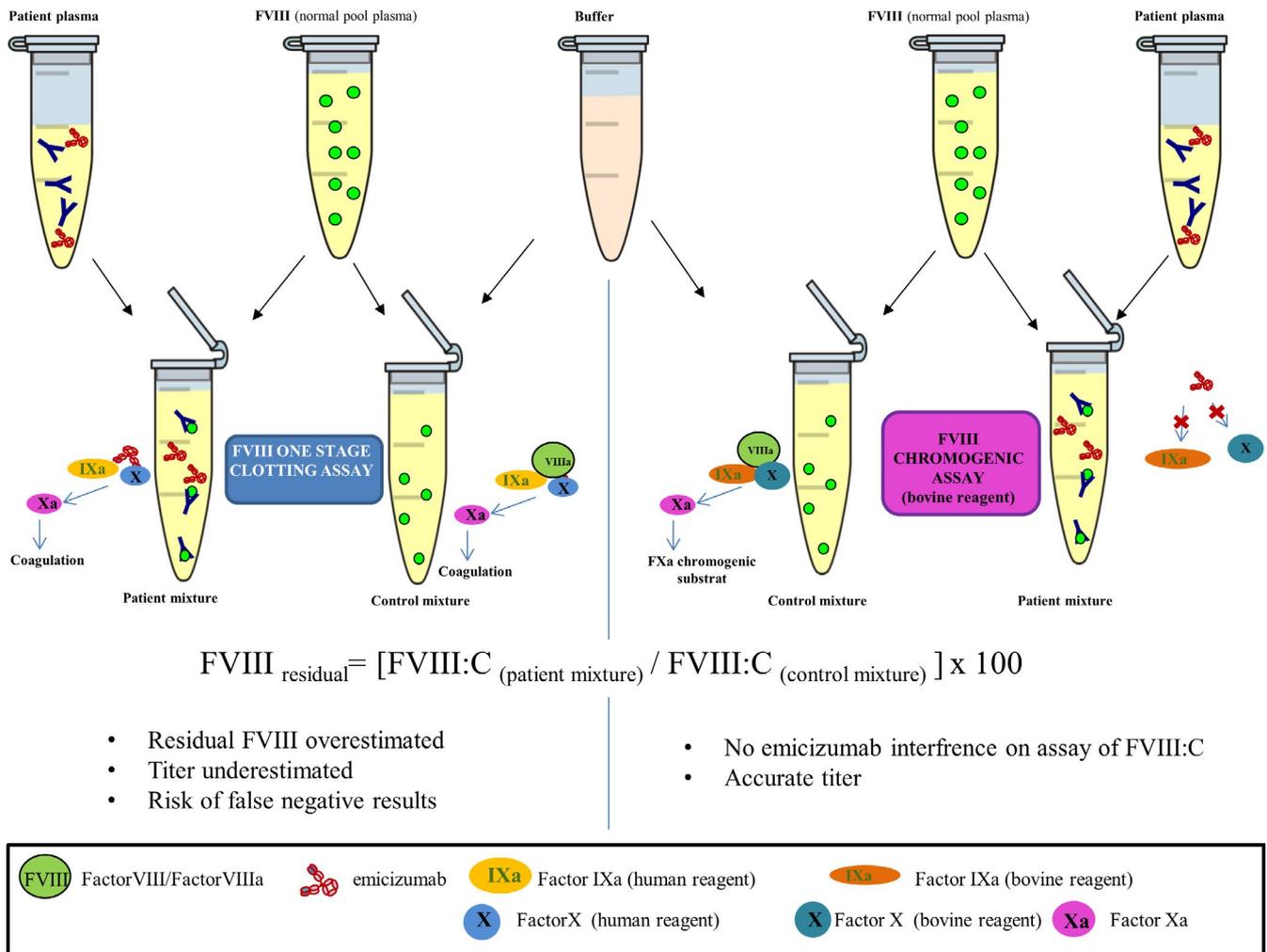


FIGURE 1 Screening and titration of an anti-VIII inhibitor by Bethesda method in the presence of emicizumab using the one-stage assay or chromogenic assay

of 15 plasma samples from non-inhibitor haemophilia A patients, treated with emicizumab, are overestimated by the one-stage assay or chromogenic method using human reagents.¹⁷ Only the chromogenic method with animal-origin reagents is suitable to determine the titre of anti-factor VIII inhibitor without interference due to emicizumab.

2.1.5 | Other haemostasis tests affected by emicizumab

All chromometric tests based on aPTT are affected by emicizumab: the anticoagulant activity of protein C and protein S determined by the chromometric technique and the activated protein C resistance ratio are underestimated. Only chromogenic assay of protein C, assay of free protein S antigen and the test for the FV Leiden mutation may be interpreted in patients during emicizumab treatment (Table 1).¹¹

2.2 | Measurement of plasma emicizumab activity

The specific emicizumab activity can be determined by using a modified aPTT-based FVIII OSA (mOSA) which has been calibrated against a specific emicizumab calibrator (r^2 diagnostics, South Bend, IN, USA). Hence, the aPTT correction in a plasma mixture from patient with FVIII-deficient plasma is proportional to emicizumab concentration. This test has been introduced in some French laboratories and is as robust as OSA FVIII assay regarding inter- and intra-assay variability coefficients of variation less than 5% respectively.¹⁵ These results were in accordance with the study of Hoffmann et al.¹⁸ Interestingly, Bowyer et al.¹³ demonstrated a good linearity with various aPTT reagents and concluded that mOSA calibrated with an emicizumab calibrator can be used to quantify the emicizumab concentration in plasma. However, in our experience, this assay is influenced by the presence of exogenous FVIII and should not be used in patients having received such therapeutic agents in combination with emicizumab.¹⁵

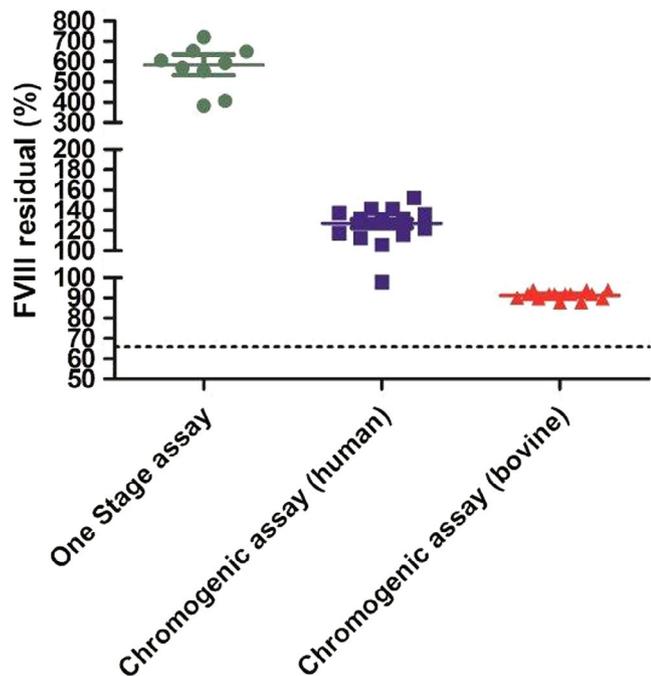


FIGURE 2 FVIII level measured in the test mixture (patient + control) compared to the control mixture obtained for 15 plasmas of haemophilia A patients without inhibitor treated with emicizumab according to the techniques used for screening and titration of an anti-VIII inhibitor by Bethesda technique¹⁷

3 | WHICH LABORATORY TESTS ARE REQUIRED TO MONITOR HAEMOSTASIS IN PATIENTS RECEIVING TREATMENT WITH EMICIZUMAB?

The different HAVEN 1, 2, 3 and 4 clinical studies showed that emicizumab prophylaxis is effective and does not require any dose adjustments, or therefore regular monitoring of haemostasis.^{3,5} However, haemostasis investigations may be necessary in certain situations summarised in Figure 3.

3.1 | Absence of clinical bleeding symptoms

In phase III study evaluating prophylaxis with a weekly subcutaneous injection of emicizumab 1.5 mg/kg after 4 loading doses of 3 mg/kg in inhibitor patients with haemophilia A over 12 years of age, the mean plasma concentrations of emicizumab were stable and around 45 µg/mL once the steady state had been reached after week five of treatment.³ Chromometric assay of emicizumab concentration, performed at the Lyon, Lille and Paris Necker centres, confirms these results, with values ranging from 30 to 80 µg/mL observed after week 5 of treatment in inhibitor patients with haemophilia A over 2 years of age (Figure 4).¹⁵ These pharmacokinetic data show

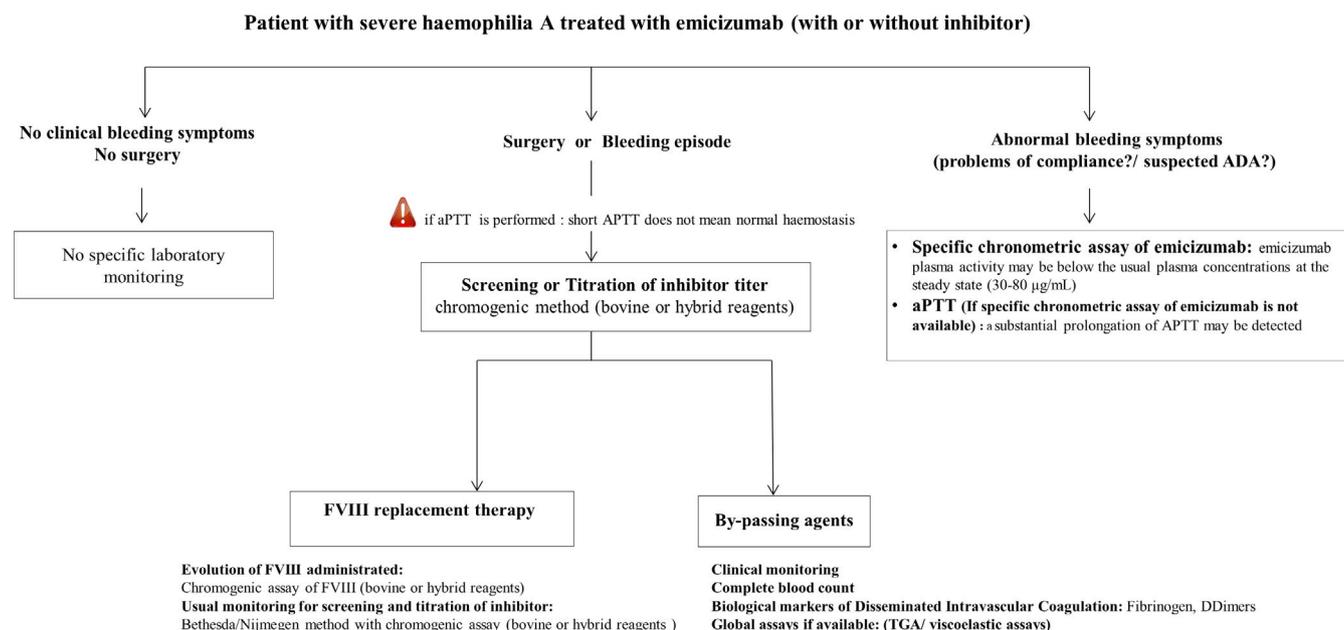


FIGURE 3 Assessing a patient treated with emicizumab according to clinical situations. Emicizumab measurement is now available in some French laboratories (Paris Necker, Lyon, Lille, Nantes, Tours) associated with haemophilia treatment centre. In these laboratories, once the calibration assay is performed, the turn-around time is the same as the FVIII OSA. If specific methods are not available (emicizumab measurement, chromogenic assay of FVIII, modified Bethesda), clinical laboratory can contact a laboratory associated with haemophilia centre (<https://mhemo.fr/>) to perform them. In the case of urgent situation (ie urgent surgery) 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 French national guidelines for the management of people with haemophilia A treated with emicizumab in case of bleeding or invasive procedures⁹

that specific monitoring of haemostasis is not necessary in the absence of bleeding symptoms or surgery.

3.2 | Surgery or bleeding episode

3.2.1 | FVIII replacement therapy

The FVIII:C measurement is recommended for dose adjustment when patients are treated with FVIII concentrate. When FVIII replacement therapy is associated with emicizumab, the use of FVIII assay method insensitive to emicizumab is mandatory. Chromogenic assay with animal-origin reagents allows accurate determination of exogenous FVIII if the assay has been verified as suitable for monitoring that concentrate.

3.2.2 | Bypassing agents

The choice of treatment will focus on the use of bypassing agents such as rFVIIa or aPCC when FVIII replacement therapy cannot be used (ie anti-FVIII inhibitor > 5 UB/mL). However, the concomitant use of aPCC with emicizumab to control bleeding has been associated with the development of thrombotic microangiopathies and venous thrombotic events. First-line treatment with rFVIIa is therefore recommended.⁹ Appropriate laboratory monitoring may be relevant when prescribing emicizumab together with a bypassing agent to ensure that the patient's haemostatic status is sufficient to allow surgery. Haemostasis cannot be monitored using conventional coagulation tests; however, several studies have evaluated the benefit of global tests, such as the thrombin generation assay (TGA)¹⁹⁻²¹ and thromboelastometry.²²⁻²⁴ In vitro and ex vivo studies have shown that the TGA is useful in selecting and adjusting doses of a bypassing agent,¹⁹ although the correlation with the clinical phenotype has yet to be validated.²⁰ In vitro studies show that thromboelastometry is sensitive to emicizumab, whether or not used in combination with

a bypassing agent. However, this only concerns studies on spiked samples, and additional ex vivo investigations are necessary in order to clarify the role of this general test in the laboratory work-up to monitor patients receiving concomitant treatment with emicizumab and a bypassing agent.

3.3 | Unusual bleeding symptoms

In the event of unusual bleeding symptoms, it is worthwhile measuring the plasma activity of emicizumab in order to determine the presence of anti-emicizumab neutralising antibodies (anti-drug antibodies, ADA), since rare cases have been described^{6,8} or to demonstrate poor treatment compliance and adherence (Figure 4).²⁵ In such situations, although aPTT is sensitive to low emicizumab concentrations,²⁶ substantial prolongation of aPTT may be detected and emicizumab plasma activity may be below the usual plasma concentrations at the steady state (30-80 µg/mL). No immunological test to characterise ADA is currently available but a recent study showed that ADA may be detected by a functional assay based on a modified version of the Bethesda assay.²⁷

4 | CONCLUSION

Treatment with emicizumab has considerably improved quality of life in inhibitor patients with severe haemophilia by simplifying prophylaxis, with weekly subcutaneous administration of the drug, and also by reducing or, indeed, removing regular laboratory tests to monitor haemostasis. The haemostasis tests, which were essential for patients receiving factor VIII replacement therapy, for dose adjustment or when patients developed inhibitors, cannot be interpreted with the usual methods in patients receiving treatment with emicizumab. aPTT normalisation with emicizumab offers false reassurance as this only reflects a moderate increase in haemostatic capacity, rather than normalisation. The knowledge of emicizumab

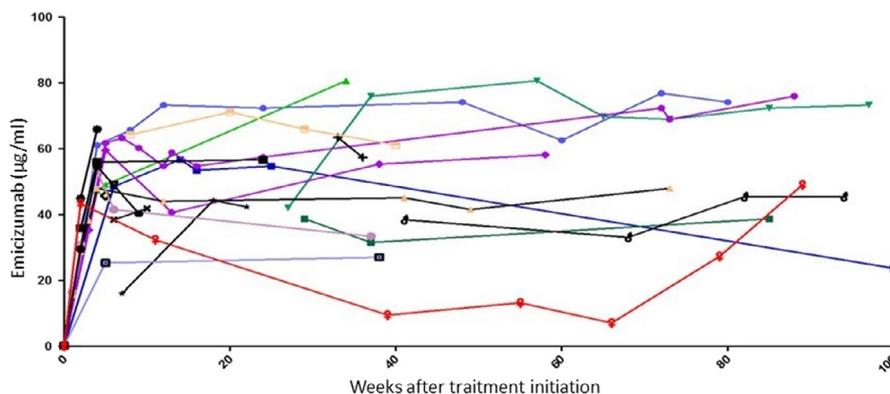


FIGURE 4 Evolution of emicizumab concentration as a function of time in 20 patients followed in 3 French centres (Lyon, Paris Necker and Lille).¹⁵ Ten weeks after treatment initiation, plasma emicizumab concentrations are 27 to 80.6 µg/mL (mean: 56.2 ± 14.8 µg/mL). An asymptomatic patient showed a transient reduction in emicizumab concentration to 7.1 µg/mL (red line), possibly due to a punctual poor compliance or transient anti-drug antibodies (ADA)

impact on haemostasis tests is essential. Our algorithm aims to select the appropriate tests in special circumstances such as surgery or bleeding events. Lastly, the development of new tests, suitable for monitoring patients in these special situations when co-administration of a bypassing agent may be necessary in order to avoid haemorrhagic or thrombotic risk, represents a new challenge for biologists in the field of haemostasis.

ORCID

Christophe Nougier  <https://orcid.org/0000-0003-0578-242X>

Emmanuelle Jeanpierre  <https://orcid.org/0000-0002-7900-0518>

REFERENCES

- Haute Autorité de Santé [Internet]. https://www.has-sante.fr/portail/jcms/c_2868847/fr/hemlibra-emicizumab-hemostatique. Accessed February 06, 2019.
- Haute Autorité de Santé - HEMLIBRA [Internet]. [cited 2020 Apr 1]. Available from https://www.has-sante.fr/jcms/p_3114482/fr/hemlibra. Accessed April 1, 2020.
- Oldenburg J, Mahlangu JN, Kim B, et al. Emicizumab prophylaxis in hemophilia A with inhibitors. *N Engl J Med*. 2017;377(9):809-818.
- Pipe SW, Shima M, Lehle M, et al. Efficacy, safety, and pharmacokinetics of emicizumab prophylaxis given every 4 weeks in people with hemophilia A (HAVEN 4): a multicentre, open-label, non-randomised phase 3 study. *Lancet Haematol*. 2019;6(6):e295-e305.
- Mahlangu J, Oldenburg J, Paz-Priel I, et al. Emicizumab prophylaxis in patients who have hemophilia A without inhibitors. *N Engl J Med*. 2018;379(9):811-822.
- Rodriguez-Merchan EC, Valentino LA. Emicizumab: review of the literature and critical appraisal. *Haemophilia*. 2019;25(1):11-20.
- Uchida N, Sambe T, Yoneyama K, et al. A first-in-human phase 1 study of ACE910, a novel factor VIII-mimetic bispecific antibody, in healthy subjects. *Blood*. 2016;127(13):1633-1641.
- Paz-Priel I, Chang T, Asikanius E, et al. Immunogenicity of emicizumab in people with hemophilia A (PwHA): results from the HAVEN 1-4 studies. *Blood*. 2018;132(Supplement 1):633.
- Susen S, Gruel Y, Godier A, et al. Management of bleeding and invasive procedures in hemophilia 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). *Haemophilia*. 2019;25(5):731-737.
- Hemlibra-epar-product-information_en.pdf [Internet]. [cited 2020 Apr 1]. Available from https://www.ema.europa.eu/en/documents/product-information/hemlibra-epar-product-information_en.pdf. Accessed April 1, 2020.
- Adamkewicz JI, Chen DC, Paz-Priel I. Effects and interferences of emicizumab, a humanised bispecific antibody mimicking activated factor VIII cofactor function, on coagulation assays. *Thromb Haemost*. 2019;119(7):1084-1093.
- Müller J, Pekrul I, Pötzsch B, Berning B, Oldenburg J, Spannagl M. Laboratory monitoring in emicizumab-treated persons with hemophilia A. *Thromb Haemost*. 2019;119(9):1384-1393.
- Bowyer A, Kitchen S, Maclean R. Effects of emicizumab on APTT, one-stage and chromogenic assays of factor VIII in artificially spiked plasma and in samples from hemophilia A patients with inhibitors. *Haemophilia*. 2020;26(3):536-542.
- Shima M, Hanabusa H, Taki M, et al. Factor VIII-mimetic function of humanized bispecific antibody in hemophilia A. *N Engl J Med*. 2016;374(21):2044-2053.
- Nougier C, Jeanpierre E, Lasne D. Posters Abstracts - 2019 - Research and practice in thrombosis and haemostasis - Wiley Online Library [Internet]. 2019. [cited 2020 Apr 1]. Available from <https://onlinelibrary.wiley.com/doi/pdf/10.1002/rth2.12229>. Accessed April 1, 2020.
- Bowyer AE, Lowe AE, Tiefenbacher S. Laboratory issues in gene therapy and emicizumab. *Haemophilia* [Internet]. 2020. May 29 [cited 2020 Jul 1]. Available from <https://onlinelibrary.wiley.com/doi/abs/10.1111/hae.13976>. Accessed July 1, 2020.
- ECTH. 2018-ABSTRACT-book.pdf [Internet]. [cited 2020 Apr 1]. Available from <http://ecth2018.org/wp-content/uploads/2018/09/ECTH-2018-ABSTRACT-book.pdf>. Accessed April 1, 2020.
- Hoffmann I, Jagdhuber F, Chen D, Davidson S, Richter N. Posters Abstracts - 2019 - Research and Practice in Thrombosis and Haemostasis - Wiley Online Library [Internet]. 2019. [cited 2020 Apr 1]. Available from <https://onlinelibrary.wiley.com/doi/pdf/10.1002/rth2.12229>. Accessed April 1, 2020.
- Dargaud Y, Lienhart A, Janbain M, Le Quellec S, Enjolras N, Negrier C. Use of thrombin generation assay to personalize treatment of breakthrough bleeds in a patient with hemophilia and inhibitors receiving prophylaxis with emicizumab. *Haematologica*. 2018;103(4):e181-e183.
- Santagostino E, Mancuso ME, Novembrino C, Solimeno LP, Tripodi A, Peyvandi F. Rescue FVIII replacement to secure haemostasis in a patient with haemophilia A and inhibitors on emicizumab prophylaxis undergoing hip replacement. *Haematologica*. 2019;2018:215129.
- Kizilocak H, Yuktman CL, Marquez-Casas E, Lee J, Donkin J, Young G. Management of perioperative hemostasis in a severe hemophilia A patient with inhibitors on emicizumab using global hemostasis assays. *Ther Adv Hematol*. 2019;10:2040620719860025.
- Hartmann R, Feenstra T, Valentino L, Dockal M, Scheiflinger F. In vitro studies show synergistic effects of a procoagulant bispecific antibody and bypassing agents. *J Thromb Haemost*. 2018;16(8):1580-1591.
- Furukawa S, Nogami K, Shimonishi N, Nakajima Y, Matsumoto T, Shima M. Prediction of the haemostatic effects of bypassing therapy using comprehensive coagulation assays in emicizumab prophylaxis-treated hemophilia A patients with inhibitors. *Br J Haematol*. 2020;1-9. <https://doi.org/10.1111/bjh.16574>
- Yada K, Nogami K, Ogiwara K, et al. Global coagulation function assessed by rotational thromboelastometry predicts coagulation-steady state in individual hemophilia A patients receiving emicizumab prophylaxis. *Int J Hematol*. 2019;110(4):419-430.
- Jenkins PV, Bowyer A, Burgess C, et al. Laboratory coagulation tests and emicizumab treatment A United Kingdom Haemophilia Centre Doctors' Organisation guideline. *Haemophilia*. 2020;26(1):151-155.
- Lenting PJ, Denis CV, Christophe OD. Emicizumab, a bispecific antibody recognizing coagulation factors IX and X: how does it actually compare to factor VIII? *Blood*. 2017;130(23):2463-2468.
- Druzgal CH, Kizilocak H, Brown J, Sennett M, Young G. Neutralizing antidrug antibody to emicizumab in a patient with severe hemophilia A with inhibitors: New case with detailed laboratory evaluation. *J Thromb Haemost*. 2020. [Epub ahead of print]
- Adamkewicz JI, Kiiialainen A, Paz-Priel I. Effects and interferences of emicizumab, a humanized bispecific antibody mimicking activated factor VIII cofactor function, on lupus anticoagulant assays. *Int J Lab Hematol*. 2020;42(2):e71-e75.

How to cite this article: Nougier C, Jeanpierre E, Ternisien C, et al. Emicizumab treatment: Impact on coagulation tests and biological monitoring of haemostasis according to clinical situations (BIMHO group proposals). *Eur J Haematol*. 2020;00:1-7. <https://doi.org/10.1111/ejh.13490>