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Emicizumab (Hemlibra®) in hemophilia A patients with inhibitors against factor VIII — guidelines of the Group for Haemostasis of the Polish Society of Haematology and Transfusion Medicine

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Summary

In this document, the Group for Haemostasis of the Polish Society of Haematology and Transfusion Medicine presents the guidelines for the use of emicizumab. Emicizumab (Hemlibra®, F. Hoffmann — La Roche, Basel, Switzerland) has been licensed for use in the European Union in 2018. In Poland, this medicinal product has been available for patients with congenital hemophilia A and inhibitors against factor VIII since March 2020. This paper is a supplement to the 2017 guidelines for management of patients with haemophilia A and B and inhibitors against factor VIII or IX.

Key words: emicizumab, haemophilia A, inhibitor, prophylaxis, bleeding, guidelines, Poland, factor VIII, by-passing agents, rFVIIa, aPCC

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Introduction

The main aim was to update the guidelines for management of patients with congenital haemophilia A and inhibitors against factor VIII following the marketing authorization of emicizumab. The guidelines were based on the published research results, and their final version was developed during consensus conferences held in the first half of 2020 with participation of the members of the Hemostasis Group of the Polish Society of Hematology and Transfusion Medicine. The guidelines are addressed primarily to health care providers directly involved in the management of patients with congenital bleeding disorders. This paper supplements the guidelines published in 2017, which discuss in detail the principles of diagnostics and treatment of haemophilia A and B patients with inhibitors [1].

Emicizumab

Emicizumab (Hemlibra®, F. Hoffmann — La Roche, Basel, Switzerland) is a recombinant, humanised, bispecific, asymmetric monoclonal antibody that bridges activated factor IX (FIXa) and factor X (FX) to restore the function of Factor VIII which is deficient in persons with hemophilia A [2, 3]. In the coagulation process emicizumab functions like activated FVIII (FVIIIa), although the two molecules show no structural similarity [4]. The completely different structure of the two molecules has a significant therapeutic benefit — the antibodies that neutralize factor VIII (FVIII inhibitors) are not capable of neutralizing emicizumab. Therefore emicizumab is able to restore thrombin generation in the plasma of patients with haemophilia A and inhibitors against FVIII.

Unlike clotting factor concentrates for intravenous use, emicizumab can be injected subcutaneously. This is another advantage much appreciated by health care professionals, but most of all by patients who avoid frequent intravenous injections. This advantage cannot be overestimated. Moreover, standard clotting factor concentrates for long-term prophylaxis are usually administered every 2–3 days, while emicizumab can be injected every 1, 2 or even every 4 weeks, depending on the selected dosing schedule [5].

Following subcutaneous administration, the mean absorption half-life of emicizumab was estimated at 1.6 days, and the absolute bioavailability of 1 mg/kg was 80.4–93.1% [2, 5]. The site of subcutaneous injection — arm, thigh or abdomen — had no effect on the pharmacokinetic parameters of emicizumab [2]. The mean elimination half-life of emicizumab is approximately 27 days [2, 5]. Such pharmacokinetic parameters of emicizumab determine its role in the management of haemophilia. Hemlibra® perfectly matches the requirements for drugs administered as part of long-term bleeding prophylaxis, but does not fully normalize the coagulation process and so cannot be used to stop acute bleeding, i.e. in treatment "on demand".

Emicizumab is injected subcutaneously once weekly, at a dose of 3 mg/kg during the first 4 weeks (loading dose) which results in the steady-state of plasma concentration of the drug. This is the so called saturation phase. In the 5th week, the mean trough plasma concentration of emicizumab in haemophilia A patients was 52.6 μg / ml [2, 5]. According to some experts, the concentration corresponds to approximately 15% of factor VIII activity; in other words, the haemostatic status of a severe haemophilia A patient on regular emicizumab dosage can be compared to that of a patient with mild haemophilia A with FVIII activity approximately 15% of normal [6]. Just like other IgG antibodies, emicizumab is catabolized by lysosomal proteolysis and eliminated [5].

Pharmacokinetic parameters of emicizumab are unaffected by age, race, inhibitor titer, mild hepatic dysfunction (max. 1.5–3 x increase of bilirubin), increase in aspartate aminotransferase level, or moderate renal impairment (creatinine clearance ≥ 30 ml/min) [2, 5].

Emicizumab doses are calculated per kg body weight (mg/kg) as the clearance and distribution volume increase in proportion to body weight (9–156 kg) [2, 5]. The pharmacokinetic profile of emicizumab for severe haemophilia A patients with inhibitors against factor VIII or without is practically the same [7]. The injection frequency at adjusted doses every 1, 2 or 4 weeks has no significant effect on the pharmacokinetic profile, with only one exception; when injected every 4 weeks, the mean Hemlibra® concentration in plasma is lower than for the product administered every 2 weeks [8].

Efficacy of emicizumab prophylaxis in patients with hemophilia A with inhibitors against FVIII

The program of clinical trials to evaluate prophylactic emicizumab involves multi-center, open-label phase 3 clinical trials, including HAVEN (1 to 4), STASEY, and HOHOEMI [9–14]. Recently, the first

Table 1. Some data for HAVEN 1 and HAVEN 2 trials [based on 9, 10]

Study population	No. of bleeds requiring treatment per 12 months* during emicizumab prophylaxis (95% CI)	% of reduced bleeding episodes during emicizumab prophylaxis vs BPAs „on demand"	% of patients with no bleeds reported during the study	% of reduced bleeding episodes during emicizumab prophylaxis vs prophylaxis with BPAs in the NIS study
HAVEN 1 Hemophilia A + inhibitor (≥ 5 UB/ml) Age: ≥ 12 years Body weight: > 40 kg In the 24-week period before the trial: ≥ 6 bleeding episodes (BPAs "on demand") or ≥ 2 bleeding episodes (BPA prophylaxis) n = 109	2.9 (1.7–5.0)	87%	Emicizumab: 63% BPAs („on demand"): 6%	79%
HAVEN 2 Hemophilia A + inhibitor (≥ 5 UB/ml) Age: < 12 years Body weight: 3–40 kg In the 24-week period before the trial: ≥ 6 bleeding episodes (BPAs "on demand") or ≥ 2 bleeding (BPA prophylaxis) n = 88	0,2 (0,06–0,62)	Not asssed	Emicizumab: 87% BPAs („on demand"): not assessed	99%

*this value is estimated as the follow-up period was < 12 months; BPAs (by-passing agents); NIS (nonintervention study) — a non-intervention study conducted before the main clinical trial

results of single-center studies have been published which report the physicians' experience with emicizumab in various clinical circumstances [15–22].

Table 1 presents the major outcome of two clinical evaluation trials on emicizumab in the management of haemophilia A patients with inhibitor against FVIII [9, 10]. Emicizumab was approved in US in 2017, also in EU, Japan and other countries in 2018 on the basis of positive results from HAVEN 1 trial [9]. The study demonstrated the superiority of emicizumab for long-term bleeding prophylaxis as compared to that of by-passing agents (BPAs) administered either prophylactically or on demand. In HAVEN 1 trial, 63% of patients on emicizumab prophylaxis reported no bleeding episodes which required hemostatic treatment, and in HAVEN 2, the percentage of such patients was even higher — 87%. Up to date, no such good results have been obtained in evaluation trials of various forms of prophylaxis in severe haemophilia, regardless of the inhibitor status. A recently published study demonstrated a markedly improved health-related quality of life as result of high efficacy of emicizumab in prevention of bleeding as well as convenience of application [23].

Safety profile of emicizumab for patients with hemophilia A with FVIII inhibitor

The HAVEN 1 trial reported thromboembolic events (TE) and thrombotic microangiopathy (TMA) episodes in 5 patients [9]. All episodes were preceded by administration of activated prothrombin complex concentrate (aPCC) at a dose of > 100 U/kg/day for > 24 h. In 4 out of 5 patients, TE and TMA symptoms resolved completely within 1–4 weeks of aPCC discontinuation. One TMA patient died, although the symptoms were reported to have resolved before death. Another TMA patient required several day intensive therapeutic plasma exchange and renal replacement therapy. In all patients, both aPCC and emicizumab were discontinued. None of the TE and TMA patients received anticoagulant medication. Two of the 4 patients resumed emicizumab therapy and no further events were reported.

The occurrence of the serious adverse events may be explained by the presence in aPCC of active and inactive forms of FIX and FX. Activated prothrombin complex concentrates (aPCC) is the basis for emicizumab to generate large amounts

Table 2. Effect of emicizumab on the results of selected coagulation assays [29–31 modified]

Assay	Results in the presence of emicizumab
APTT	At trough concentrations of emicizumab (> 5 μg/ml) APTT completely normalized
Activity of clotting factors VIII, IX, XI and XII in a one-stage clotting assay (based on APTT)	Activity over-responsive (even up to several thousand %)
APTT correction assay	False positive result, no inhibitor
Factor VIII inhibitor titration based on APTT	False positive result, no inhibitor
PT	Uneffected (or slightly prolonged) — reliable assay
Activity of clotting factors II, V, VII and X in a coagulation test (based on PT)	Most likely reliable
Fibrinogen (Clauss method)	Most likely reliable
TT	Most likely reliable
Factor VIII activity by chromogenic method with human reagents (factors IXa and X)	Over-responsive
Factor VIII activity by chromogenic method with bovine reagents (factors IXa and X)	Reliable result
Factor VIII inhibitor titer in chromogenic assay with bovine reagents	Reliable result

APTT — activated partial thromboplastin time; PT — prothrombin time; TT — thrombin time

of thrombin which may lead to thromboembolic complications [24]. A mechanism of TMA development in which enhanced thrombin generation does not seem to play the primary role has not yet been described. It is worth mentioning that one severe haemophilia A patient with inhibitor, who received recombinant activated factor VII (rFVIIa) during emicizumab prophylaxis, experienced myocardial infarction without ST-segment elevation and pulmonary embolism [25]. Up to date however, no thromboembolic complications or TMA cases have been reported for hemophilia A patients with inhibitor during concomitant administration of emicizumab and factor VIII concentrates [26, 27].

Subcutaneous Hemlibra® injections are well tolerated, although 22% of study patients reported mild or moderate skin irritation at injection site [2, 5]. Only one patient discontinued emicizumab due to severe drug-induced hypersensitivity [2, 5].

Emicizumab is an immunogenic protein that can stimulate the recipient's immune system to produce the so called anti-drug antibodies (ADA). In the whole HAVEN trial, 14 out of 398 (3.5%) patients developed ADA, and 3 (< 1%) developed neutralizing anti-drug antibodies to emicizumab [28]. One pediatric hemophilia A patient with inhibitor developed anti-drug antibodies that completely eliminated the pharmacokinetic effect of emicizumab. It was therefore necessary to go back to BPAs [10].

Laboratory testing of inhibitor patients on emicizumab prophylaxis

Table 2 presents the effect of emicizumab on the parameters of selected laboratory coagulation tests [29–31]. Emicizumab reduces the activated partial thromboplastin time (APTT) and may therefore be responsible for false APTT-dependent coagulation assay results, factor VIII activity included. In severe haemophilia A patients normalization of the APTT will occur, even at minimum concentration of emicizumab in plasma (> 5 μg/ml). Emicizumab has little effect on prothrombin time (PT) and practically no impact on thrombin time (TT) and fibrinogen concentration in plasma measured with Clauss method. The effect of emicizumab on PT is minimal, therefore the results of PT-dependent coagulation tests are considered reliable. Guidelines for determination of FVIII activity, titration of inhibitors to FVIII and measurement of other hemostatic parameters as well as interpretation of results for patients on emicizumab prophylaxis are presented later on in the paper and in Table 3.

Emicizumab in Poland

In accordance with the provisions of the National Program for Treatment of Patients with Hemophilia and Related Hemorrhagic Disorders (2019–2023), emicizumab prophylaxis was launched in 2020 in a group of 30 severe haemo-

Table 3. Practical guidance on various laboratory assays during emicizumab prophylaxis [29–31 modified]

Assay	Guidance
FVIII activity	Recommended use of chromogenic method with bovine reagents Following positive verification in local laboratory, kits for determination of FVIII activity by chromogenic assay with human factor IXa and bovine factor X may be appropriate
FVIII inhibitor titer	It is recommended to use the chromogenic method with bovine factors IXa and X. The same method should be used for inhibitor titration in the blood sample collected prior to inclusion of emicizumab, in order to facilitate the interpretation of results in long-term monitoring Following positive verification in a local laboratory, kits for determination of FVIII activity by chromogenic assay with human factor IXa and bovine factor X may be appropriate
ADA	No available commercial test for ADA. In the case the neutralizing ADA are suspected, it is recommended to control emicizumab levels (see below)
Emicizumab concentration	It is recommended to use a test based on the measurement of FVIII activity with one-stage clotting assay with specific emicizumab calibrators to which the results are referred

ADA — anti-drug antibodies

philia A patients with high titre inhibitor against factor VIII. For Polish hemophilia A patients with no inhibitor Hemlibra® is not as yet available. Eligibility criteria for long-term bleeding prophylaxis with emicizumab are set forth in the National Program (https://www.gov.pl/web/zdrowie/narodowy-program-leczenia-chorych-na-hemofilie-i-pok Related-skazy-krwotocze-) for the years 2019–2023.

Guidance for management of patients with hemophilia A and inhibitors against factor VIII in selected clinical circumstances

There are well justified hopes for the improvement of the efficacy of haemophilia A management with emicizumab. Data from clinical trials clearly indicate that many patients on regular emicizumab prophylaxis report no bleeding episodes, though the so-called breakthrough bleeds (i.e. bleeding despite prophylaxis) may obviously occur in some of them. Moreover, emicizumab alone does not provide sufficient anti-haemorrhagic protection, especially where major invasive surgery is required. The cover of additional hemostatic agents is often necessary. As mentioned previously, the HAVEN 1 trial reported severe thrombotic complications in patients on concomitant emicizumab and aPCC therapy [5, 9]. It is therefore crucial to select an additional hemostatic agent at adjusted dosage for a patient receiving emicizumab [32–35]. There may also appear problems with interpretation of coagulation test results for such patients because emicizumab effects the APTT measurement. Selection of appropriate laboratory assay for monitoring haemostatic parameters may also be a challenge in everyday clinical practice [29–31].

In the last section of the paper the Group for Haemostasis of the Polish Society of Haematology and Transfusion Medicine presents guidelines for the use of emicizumab in haemophilia A patients with factor VIII inhibitor in various clinical circumstances.

I. General information on the use of emicizumab in haemophilia A patients with inhibitors against factor VIII

1. The healthcare provider should inform the patient to carefully follow instructions regarding the use of emicizumub, to strictly adhere to the calculated dose and the injection schedule. The patient should also be cautioned about potential side effects and interactions with other drugs, especially with aPCC. Helpful information are presented in the leaflets/brochures "Guide for patient/healthcare provider" and "Patient Alert Chart", issued by Roche Polska Co. Ltd.
2. Inhibitor bypassing agents should be discontinued at least 24 hours prior to the first emicizumab injection. This recommendation is based on TE and TMA episodes reported during the HAVEN 1 study when emicizumab was administered concomitantly with aPCC at doses > 100 U/kg for > 24 h.
3. Haemophilia A patients with inhibitors against factor VIII considered for emicizumab prophylaxis who are scheduled for major surgery under cover of BPA in the next months, are recommended to go through the procedure

first and then to start emicizumab prophylaxis. This recommendation stems from the concern that in the absence of an adequate haemostatic response to rFVIIa, it would be necessary to administer aPCC which would only increase the risk of TE or TMA.

4. Before starting emicizumab prophylaxis, inhibitor titration should be performed. In low-titre patients (< 5 Bethesda units/ml) when heavy bleeding occurs during emicizumab therapy, factor VIII concentrate may be administered under control of factor VIII plasma activity. The specific principles for management are presented in detail in sections II and VI.
5. The efficacy of emicizumab in long-term prophylaxis should be systematically evaluated. Frequent "breakthrough bleeds" raise suspicion of the presence of emicizumab neutralizing antibodies and that calls for appropriate diagnostic laboratory assays (see section V).
6. The patient's weight should be monitored regularly and the emicizumab dose adjusted accordingly.
7. Every patient should have immediate access to sufficient amounts of BPA and/or FVIII concentrate for "breakthrough bleeds" (see section II).
8. Heavy breakthrough bleeds or symptoms suggestive of thromboembolic event or thrombotic microangiopathy are indications for immediate hospitalization in a haemophilia treatment center.
9. Every Polish patient with a congenital bleeding disorder should have a *Management chart* which provides all relevant information regarding emicizumab therapy.

II. Management of acute bleeding in inhibitor patients on emicizumab prophylaxis

1. In the event of life or limb-threatening bleeds, the patient on emicizumab prophylaxis must immediately be given rFVIIa at a dose of 90–120 μg/kg and promptly transferred to a haemophilia treatment center for further management.

   The drug of choice to arrest bleeding in most recent high-titre patients is rFVIIa at a standard dose, according to Polish guidelines of 2017 [1]. "Mega doses" of rFVIIa, ie 270 μg/kg are not recommended.

   If administration of rFVIIa fails to stop massive bleeding, it is necessary to use aPCC at an initial dose of not more than 50 U/kg. Subsequent (small) doses should be injected every 8–12 hours with the daily dose not exceeding 100 U/kg. Treatment must proceed under strict supervision of the haemophilia center. If administration of aPCC is to be continued for > 24 h, close observation of the patient should be supported by daily monitoring of laboratory parameters for TE, disseminated intravascular coagulation (DIC) and TMA, i.e. D-dimer, fibrinogen, platelet count, tests for hemolysis (lactate dehydrogenase (LDH), bilirubin and haptoglobin, reticulocytes), ADAMTS13 activity, peripheral blood smear (particularily for schistocytes) and assessment of renal function.

   Comment 1: in the HAVEN 1 trial, thromboembolic events and TMA were described only in patients who receivied emicizumab in concomitance with aPCC at a dose > 100 U/kg for > 24 h. In the HAVEN program, there were no reports on thromboembolic events or thrombotic microangiopathy in patients on emicizumab prophylaxis in concomitance with rFVIIa. Outside the clinical trials however, one case of thromboembolic complications was reported in a patient who was on emicizumab prophylaxis after rFVIIa administration) [25].

   Comment 2: according to isolated literature reports even very low doses of aPCC (20 U/kg) administered during emicizumab prophylaxis may be sufficient to stop bleeding [20]. These reports however are no recommendation for the use aPCC at such doses.

   Comment 3: emicizumab has a long biological half-life therefore it is present in the patient's organism up to 6 months of discontinuation. The recommendations regarding careful use of aPCC should therefore apply not only to patients on regular emicizumab prophylaxis, but also to those who discontinued emicizumab injections within the last 6 months.

   In patients with most recent low inhibitor titre (< 5 Bethesda units/ml), the treatment of choice for life and limb-threatening bleeds is FVIII concentrate provided adequate factor VIII activity in plasma is achieved. In high responders (HR) i.e. those with large amounts of antibodies to factor VIII following exposure to FVIII, the inhibitor titer will increase (anamnestic response) within 5–7 days of administration to a value that precludes effective treatment of bleeding with FVIII concentrate. Since that moment, BPAs should be used in accordance with the previously presented guidelines.

Comment 1: It is common belief that in order to stop bleeding it is better to achieve therapeutic FVIII activity in plasma than to administer BPAs.

Comment 2: When exposure to FVIII is avoided, the inhibitor titer may fall back to < 5 Bethesda U/mL within several months of the anamnestic response which allows for the re-use of FVIII concentrate in the event of severe bleeding.

Comment 3: In the HAVEN trial, none of the haemophilia A patients with inhibitor against factor VIII who were on emicizumab prophylaxis in concomitant use with FVIII developed thromboembolic events or thrombotic microangiopathy.

2. For minor bleeding episodes which are not life or limb — threatening, rFVIIa is the treatment of choice for patients with haemophilia A with inhibitors against FVIII on emicizumab prophylaxis, regardless of their most recent inhibitor titre. Standard doses of rFVIIa (90–120 μg/kg) are recommended, while the so-called "mega doses", ie 270 μg/kg are not.
   If rFVIIa is unavailable or its use does not bring the expected clinical effect, aPCC should be administered. The initial aPCC dose should not exceed 50 U/kg. If rFVIIa or aPCC are administered as part of home treatment, any breakthrough bleeding should be immediately reported to the hemophilia treatment center. If breakthough bleeding is not resolved with 2–3 doses of rFVIIa, requires > 1 dose of aPCC or is the cause of patient's anxiety, management must be continued in a haemophilia treatment center where bleeding classification is corrected (from mild to severe) and treated according to the previously presented recommendations.

Comment 1: it is suggested that the patient has access to sufficient home supply of rFVIIa (sufficient for at least 3 doses of 90–120 μg/kg).

Comment 2: If a patient is known to have a weaker clinical response to rFVIIa than to aPCC, a home supply of aPCC at a single dose of 50 U/kg is admissible.

Comment 3: rFVIIa concentrate contains no factor VIII therefore it never induces an anamnestic response in patients with haemophilia A and inhibitors against factor VIII.

Comment 4: aPCC concentrate with residual amounts of factor VIII induces an anamnestic response in approximately 20–30% of patients with haemophilia A and inhibitors against factor VIII.

3. Recombinant porcine factor VIII (rpFVIII, Obizur®, Takeda) may represent an option to control bleeding in a haemophilia A patient with inhibitors against FVIII and on emicizumab prophylaxis. However, this drug is licensed only for the treatment of bleeding in patients with acquired haemophilia A (AHA) and its use in congenital haemophilia A would be experimental.

Comment: recombinant porcine FVIII is not covered by the reimbursement in Poland, so this drug in our country is currently practically unavailable.

4. A breakthrough bleeding is no indication to change the regimen of emicizumab prophylaxis, either the dose or injection frequency. Frequent breakthrough bleeding however, arouses suspicion of anti-emicizumab antibodies. This should be verified with appropriate laboratory assays (see section V).
5. Emicizumab injections are no contraindication to the use of antifibrinolytics drugs (e.g. tranexamic acid) and local haemostatics (e.g. fibrin glue or platelet gel), if necessary. A patient on emicizumab prophylaxis can also take tranexamic acid together with rFVIIa.

III. Management of an invasive procedure or surgery in patients with haemophilia A and inhibitors against factor VIII on emicizumab prophylaxis

1. Most minor procedures (central venous catheter insertion/removal, uncomplicated single dental extractions, endoscopies with biopsies) can be safely performed even without additional haemostatic drugs. However, patients undergoing such procedures must be carefully monitored for bleeding complications. In the perioperative period, BPAs must be readily accessible in case of bleeding complications.

Comment 1: if in doubt as to perioperative bleeding risk, a single dose of rFVIIa (90–120 μg/kg) should be administered prior to the procedure.

Comment 2: Tranexamic acid in monotherapy at an intravenous dose of about 10 mg/kg or an oral dose of 15–25 mg/kg every 8 hours is an effective protection against excessive bleeding, especially during invasive procedures at mucosal sites, e.g. after tooth extraction.

Comment 3: FVIII concentrates are not recommended as cover for minor invasive procedures in HR patients with recent low inhibitor titer; several months after exposure to FVIII the antibody titre is still high which precludes its use when it is particularly desirable, e.g. in life-threatening bleeds or for hemostatic cover of major surgical procedures, and — as already mentioned

— bleeding can be stopped more effectively with achieving therapeutic FVIII activity in plasma than by administration of BPAs. The only exception are situations when bleeding complications occur despite the use of BPAs. FVIII concentrate should then be given under control of FVIII activity in the patient's plasma.

2. Major invasive procedures in most recent high-titre patients should be performed under cover of rFVIIa applied at standard doses, according to Polish guidelines of 2017 [1].

Comment 1: In this group of patients epidural and spinal anesthesia should be avoided, if possible.

Comment 2: There are no contraindications to concomitant use of rFVIIa and tranexamic acid.

3. Major invasive procedures in recent low-titre patients (< 5 Bethesda units/ml) should be performed under cover of FVIII concentrate provided the therapeutic factor VIII activity in plasma is achieved. In HR patients, 5–7 days after administration of FVIII concentrate, the inhibitor titre will increase to a value which precludes effective perioperative antihaemorrhagic prophylaxis with FVIII concentrate. It is necessary to administer BPAs (rFVIIa first).

Comment: achieving therapeutic FVIII plasma activity is more effective than therapy with BPAs.

4. In the case of excessive perioperative bleeding in a recent high-titre patient who is given rFVIIa as cover for major surgery, aPCC should be considered at a total daily dose of < 100 U/kg (a single aPCC dose should not exceed 50 U/kg). If aPCC has to be administered for > 24 h, the minimum effective doses are suggested not exceeding the total daily dose of 100 U/kg. Management must proceed under strict supervision of the haemophilia treatment center. In addition to close clinical observation, laboratory parameters should be monitored for TE, disseminated intravascular coagulation (DIC) and TMA, i.e. D-dimer, fibrinogen, platelet count, tests for hemolysis (lactate dehydrogenase (LDH), bilirubin and haptoglobin, reticulocytes), ADAMTS13 activity, peripheral blood smear (particularily for schistocytes) and assessment of renal function.

Comment 1: the concomitant use of aPCC and tranexamic acid is discouraged in patients on emicizumab prophylaxis.

5. rpFVIII is a drug that could be used as cover in major surgery for haemophilia A patients with FVIII inhibitor and on emicizumab prophylaxis. This drug however is licensed for the treatment of bleeding in AHA patients only. Its use in congenital haemophilia A would be experimental.

Comment: recombinant porcine FVIII is not reimbursed in Poland, so currently in our country this drug is unavailable.

6. If elective surgery for a haemophilia A patient with FVIII inhibitor on emicizumab prophylaxis can be postponed for several months, it is suggested to discontinue emicizumab prophylaxis and proceed with surgery only after complete elimination of emicizumab from the patient's organism.

Comment 1: emicizumab remains active in the patient's body for up to 6 months following discontinuation.

Comment 2: This recommendation arises from the risk of thromboembolic events and thrombotic microangiopathy in patients on emicizumab prophylaxis who might require aPCC in the perioperative period.

IV. Emicizumab and ITI

1. In the management of severe haemophilia A patients with inhibitors against FVIII the major goal is immune tolerance induction (ITI) to factor VIII with protocols listed in the Polish guidelines published in 2017 [1]. Emicizumab should therefore be considered for patients who have failed or cannot achieve ITI, e.g. due to a lack of venous access.
2. Patients undergoing ITI may experience bleeding. If bleeding episodes are frequent, antihaemorrhagic prophylaxis is recommended — mainly with aPCC, less often with rFVIIa before emicizumab is administered. Emicizumab may also be used to prevent bleeding in such circumstances. The advantages of emicizumab over aPCC and rFVIIa are the subcutaneous route of administration and high efficacy of bleeding prevention.

Comment 1: The experience with emicizumab administered to patients on ITI regimen is rather limited, therefore no specific ITI protocol can — as yet — be recommended.

Comment 2: FVIII activity and inhibitor titre in patients on emicizumab prophylaxis are assayed with chromogenic method and bovine reagents (see section V).

V. Laboratory tests for haemostasis in haemophilia A patients with inhibitor on emicizumab prophylaxis

1. The medical team supervising the patient on emicizumab prophylaxis as well as laboratory workers must be well aware of the impact of

emicizumab on laboratory assays (Table 1). Misinterpretation of laboratory findings may lead to incorrect diagnosis and therapeutic decisions.

2. APTT measurement is not intended for monitoring of emicizumab prophylaxis. However, prolonged APTT in a patient on emicizumab prophylaxis may either indicate failure to adhere to injection schedule or the presence of ADA which reduce emicizumab plasma levels to < 5 μg/ml.
3. To determine FVIII activity when emicizumab and human factor VIII are used concomitantly it is recommended to use the chromogenic assay with bovine reagents (Table 3).
4. To determine the titre of inhibitor to factor VIII for a patient on emicizumab prophylaxis it is recommended to use the chromogenic assay with bovine reagents (Table 3).
5. If anti-emicizumab antibodies are suspected, it is possible to measure emicizumab concentration in patient's plasma (Table 3). It is recommended to use a test based on the measurement of FVIII activity with one-stage clotting assay with specific emicizumab calibrators to which the results are referred.
6. Further studies are required to determine the role of global hemostatic tests (thromboelastometry and thromboelastography) and measurement of thrombin generation in the monitoring of patients on emicizumab prophylaxis.

VI. Thromboembolic events (TE) and thrombotic microangiopathy (TMA)

1. Development of TE or TMA may be life-threatening. The patient must be hospitalized.
2. APCC should be discontinued immediately if there is strong suspicion or confirmation of TE or TMA.
3. Once the TMA diagnosis is confirmed, plasmapheresis procedures should be considered together with other therapies adapted to the patient's clinical condition (e.g. renal replacement therapy, correction of haemolytic anemia, etc.).

Comment: in the HAVEN trial emicizumab has been reported to remain in the patient's body for > 3 months (observation of J.W.) despite discontinuation of emicizumab prophylaxis and following several plasmapheresis procedures for TMA.

4. Administration of rFVIIa should be considered if TE/TMA coexist with active bleeding, in patients with a recent high FVIII inhibitor titre. In patients with recent low inhibitor titres human factor VIII concentrate should be considered under control of clotting factor activity.

Comment 1: in the HAVEN trial, no TE and TMA episodes were observed in patients with concomitant use of emicizumab and rFVIIa or emicizumab and FVIII (although, outside clinical studies, one case of thromboembolic complications was reported in a patient on emicizumab prophylaxis following rFVIIa administration) [25].

Comment 2: According to some experts in such clinical circumstances rFVIIa can be used in smaller doses, eg.45 μg/kg [33].

5. Up-to-date clinical findings indicate that most TE and TMA cases induced by the concomitant use of emicizumab and aPCC, do not require anticoagulant therapy.
6. Anticoagulant therapy markedly increases the risk of severe bleeding in haemophilia patients with inhibitor, even during administration of emicizumab and/or BPAs. Anticoagulants are therefore recommended only for severe thromboembolic events.

Comment: anticoagulant therapy should be as short as possible, and anticoagulants should be discontinued if bleeding becomes more intense.

Final remarks

Introduction of emicizumab to the management of hemophilia A patients with or without inhibitors against VIII is a real breakthrough. Emicizumab is extremely effective for long-term prophylaxis of bleeding, and unlike clotting factor concentrates it is injected subcutaneously.

Emicizumab has been in use for Polish haemophilia A patients with inhibitors against factor VIII since March 2020 (until the date emicizumab was available only for patients enrolled in clinical trials). Although excellent therapeutic effects are to be expected in most, if not all patients treated with emicizumab, it must be noted that there are certain differences between emicizumab therapy and treatment with BPAs. In this paper we discuss the safety of concomitant use of emicizumab and aPCC, the principles of management of bleeds during emicizumab prophylaxis as well as guidelines for management of patients on emicizumab therapy and subjected to invasive procedures. The paper also provides practical guidance for selection of laboratory tests appropriate for monitoring the efficacy and safety of emicizumab as well as comments on the potential role of the drug for bleeding protection under ITI.

Emicizumab prophylaxis must be supervised by expert comprehensive care teams consisting of physicians, nurses, and laboratory diagnosticians from haemophilia treatment centers. The authors of the paper express sincere hope that the presented guidelines will serve as support for the supervision to be more effective.

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