

# Emicizumab for All Pediatric Patients with Severe Hemophilia A

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## Abstract

Emicizumab is the first approved nonreplacement therapy for bleeding prophylaxis in hemophilia A (HA) patients. In 2018, it was licensed for HA patients with inhibitors, subsequently followed by an “European Medicines Agency (EMA)” approval for patients with severe HA in the absence of inhibitors in 2019. This is immediately raising the question whether emicizumab is suitable as a first-line treatment for all pediatric patients with severe HA. In this review, we want to discuss what we have, what we know, and what we would like to know. Severe HA is characterized by severe spontaneous and traumatic bleedings, particularly into muscles and joints leading to chronic joint damage. Standard of care is the regular, prophylactic replacement of factor VIII to prevent bleedings. Due to approval of emicizumab—the first nonreplacement therapy for bleeding prophylaxis—in HA patients with inhibitors, and severe HA patients without inhibitors, it is of pivotal interest whether emicizumab could be the first-line treatment in all pediatric patients with severe HA. Clinical trials and real-world observational studies could demonstrate a good efficacy and safety for bleeding prevention during emicizumab treatment in HA patients with and without inhibitors. This clearly indicates that emicizumab could improve HA treatment. However, some crucial and critical questions are remaining with regard to the use of emicizumab. Some of this missing information is already under investigation in the context of clinical trials. Until getting finalized data to shed insights into the points that are currently being discussed, there is a variety of expert and expert group recommendations, which are tackling questions concerning the treatment of HA patients. This review will address major information that is already available, but will also focus on important points that remain to be elucidated in the context of HA treatment.

## Keywords

- ▶ emicizumab
- ▶ children
- ▶ PUP
- ▶ ITI

## Hemophilia A

Hemophilia A (HA) is an X-linked bleeding disorder with a reduced or missing factor VIII (FVIII) activity. Severe HA, defined as a deficiency of FVIII with an activity <1%, is characterized by severe spontaneous and traumatic bleedings, particularly into muscles and joints leading to chronic joint damage, also life-threatening bleedings can occur.

In the context of a known family history, patients with HA (PWHAs) can often be diagnosed shortly after birth, whereas patients without a positive family history (~30%) are diagnosed significantly later. The median age of the diagnosis of severe HA is 15 months.<sup>1–3</sup> The median age of the first joint bleeding is reported to be in the range of 18 to 20 months.<sup>1–3</sup> In these patients, standard of care is a regular prophylaxis with intravenous FVIII concentrates (clotting factor concentrates [CFC]) to prevent joint damage. It is recommended to

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start prophylaxis as soon as possible, ideally within the first 2 years of life, and before occurrence of the first joint bleeding.<sup>1,2</sup>

Prophylaxis with CFC can be started with a full prophylaxis (three times per week, or every other day), or with a frequency of only once weekly. This schedule can then be increased to a full prophylaxis regimen, depending on the frequency of bleeding events. The initial dose has been reported to be 250 to 500 IU (International Units).<sup>2</sup> The advantage of the once weekly schedule is to avoid the implementation of a central venous access device (CVAD), and to reduce the risk of inhibitor development. By contrast, the disadvantage of this schedule is that bleeding prevention is not completely achieved.<sup>1,2,4</sup> Due to the short half-life of FVIII (8–12 hours), administration of a standard half-life (SHL) FVIII concentrates is required at least three times per week, or every other day to achieve “full prophylaxis.” By the use of extended half-life products (EHLs), the frequency could be decreased up to twice weekly. However, this reduced schedule may be insufficient in younger children due to the shorter half-life, and higher physical activity, as well as injury level of children.<sup>1</sup>

Another rare, but serious and potentially life-threatening, complication of severe HA is the intracranial hemorrhage (ICH). The incidence of ICH beyond neonatal period was reported with up to 7 per 1,000 patient-years.<sup>5,6</sup> ICHs are observed more frequently in younger children (especially <2 years) without prophylaxis.<sup>5–7</sup> Regular full prophylaxis halves the risk of ICH.<sup>5,8</sup> Anderson et al reported an incidence of 1.7/100 patient-years in patients with no prophylaxis, versus 0.033/100 patient-years for patients with full prophylaxis, or 0.5/100 patient-years for patients with partial prophylaxis.

The current prophylaxis with intravenous CFC is very effective to protect patients, and to allow an almost normal participation in daily life. Early initiation of prophylaxis provided continued protection against joint damage when compared with a delayed start.<sup>9</sup> However, even the start of an early prophylaxis was not sufficient to fully prevent joint damage, and cannot completely prevent long-term joint disease.<sup>9,10</sup> Accordingly, 35% of patients in the cohort investigated by Warren et al demonstrated osteochondral damages in MRI at the age of 18, despite early prophylaxis.<sup>9</sup> In line with these findings, in a Bonn cohort, 90% of patients treated with an intensive prophylactic regimen exhibited a joint disease at the age of 30 to 40 years.<sup>10</sup> In earlier treatment protocols, a trough FVIII level of greater than 1% was recommended. In current guidelines, a trough level of greater than 3 to 5% is thus recommended to achieve a better joint protection.<sup>11,12</sup> This becomes feasible due to the availability of EHLs.

The development of neutralizing antibodies (inhibitors) against FVIII is one of the most severe complications in modern therapy of severe HA, leading to ineffectiveness of FVIII substitution, an increased bleeding risk, mortality, and morbidity. Around 30% of patients with severe HA develop inhibitors to FVIII.<sup>13–16</sup> As treatment with FVIII is not effective in these cases, bypassing agents (BPAs) such as recom-

binant FVIIa (rFVIIa), or activated prothrombin complex concentrate (aPCC), were used for bleeding prophylaxis and/or treatment in patients with inhibitors. The treatment with rFVIIa or aPCC is effective in around 80% of these patients, while almost one-third of patients benefit from treatment with either BPA or sequential therapy.<sup>17–21</sup>

Usually, patients with inhibitors were treated with immune tolerance induction (ITI) to eradicate the inhibitors, and to establish immune tolerance. However, the therapy is extremely demanding and expensive. The success rate of different ITI protocols varies from 53 to 91% in different studies.<sup>22–24</sup> In a multicenter retrospective cohort study, a relapse frequency of approximately 30% was described in patients after successful ITI, independently of adherence to post-ITI FVIII prophylaxis. Risk factors for recurrence of neutralizing antibodies were recovery rates less than 85% at end of ITI, and immune-modulating treatments during ITI.<sup>25</sup>

## Emicizumab

Emicizumab was licensed for bleeding prophylaxis in PWH with inhibitors, or in patients with severe HA in the absence of inhibitors, and is thus the first approved nonreplacement therapy (NRT). Of note, emicizumab is not appropriate for the treatment of acute bleedings.

Emicizumab is a bispecific humanized monoclonal antibody bridging activated FIX and FX, thus mimicking function of activated FVIII. Due to this mechanism of action, severe HA is changed into a mild form with an estimated FVIII activity of at least 9%.<sup>26</sup>

Emicizumab has to be administered subcutaneously. After a loading phase of 4 weeks with a dose of 3 mg/kg body weight (BW) weekly (QW), the maintenance therapy can be performed with 1.5 mg/kg BW weekly (QW), 3 mg/kg every 2 weeks (Q2W) or 6 mg/kg BW every 4 weeks (Q4W). In pharmacokinetic analyses, the plasma trough concentration of >30 µg/mL was sustained in all dose schedules over time. However, in the Q4W schedule, the mean levels were slightly lower than in more frequent dose regimens. Similarly, children enrolled in HAVEN 2 showed mean trough concentrations of approximately 50/48/38 in the QW/Q2W/Q4W, respectively.<sup>27</sup>

Efficacy, safety, and pharmacokinetics were proofed in several phase 3 clinical trials (HAVEN 1: adults/adolescents >12 years with inhibitors [QW schedule]; HAVEN 2: pediatric patients <12 years with inhibitors [QW, Q2W, Q4W schedules]; HAVEN 3: adults/adolescents >12 years without inhibitors QW, Q2W schedules); HAVEN 4: adults/adolescents >12 years with and without inhibitors Q4W schedule]). Emicizumab prophylaxis resulted in a markedly reduced annual bleeding rate (ABR). Similarly, the number of patients requiring no bleeding related treatment was high (56–90%).<sup>28–31</sup> Analysis of the long-term outcome with emicizumab prophylaxis in patients enrolled in HAVEN 1–4 ( $n = 391$ ) showed a model-based ABR of 1.4, across a median efficacy period of 120.4 weeks (89–164.4). Over time, ABR further declined with a mean treated ABR of

0.7 at weeks 121 to 144 ( $n=170$ ). In this period, 82.4% of patients required no bleeding-related treatments.<sup>31</sup> The longest observation time of 5.8 years was reported from PWHA enrolled in phase 1, and phase 1/2 dose finding trials. These patients were first treated with 0.3 mg/kg, 1 mg/kg, or 3 mg/kg QW, and then switched to emicizumab (1.5 mg/kg QW) after its approval. This long-term observation could show the remarkable efficacy as well as safety of emicizumab, and thus highlights the improvement with regard to the severity and quantity of bleeding-associated symptoms, daily life, and mental health.<sup>32</sup>

### Laboratory

The use of emicizumab requires some adjustments to the well-established monitoring techniques that are currently being used in HA treatment.<sup>33</sup> It has a considerable shortening effect on the aPTT, and is thus influencing aPTT-based coagulation assays, as the one-stage FVIII assay (OSA). Consequently, the Bethesda assay, which relies on this OSA technique, cannot be used for analyzing FVIII inhibitors during emicizumab treatment. Misinterpretation of such results could increase the safety risk for patients. The interference with coagulation assays is persisting up to 6 months after discontinuing emicizumab treatment. However, parameters such as thrombin time, chromogen assays (protein C, plasminogen, antithrombin), fibrinogen assays, and other immunoassays, as well as ELISAs do not show any interference.<sup>33</sup>

For measurements of FVIII activity and FVIII inhibitors, bovine chromogenic FVIII assays and chromogenic Bethesda assays (bovine protein based) are necessary. The modified OSA calibrated against emicizumab may be used for measurements of emicizumab plasma levels.<sup>33</sup> However, these assays are usually exclusively offered in large specialized laboratories, which is an obstacle that needs to be taken into consideration while, for instance, planning surgeries.

### Safety

Injection-site reactions were the most frequent reported side effects in 10 to 22% of all cases. However, they have been usually described as mild and self-limited.<sup>28–31,34</sup>

Collectively, in the HAVEN trials, six participants suffered from treatment-related severe adverse events: cavernous sinus thrombosis, neutralizing antibodies, skin necrosis, and superficial thrombophlebitis (one each) and three thrombotic microangiopathies (TMAs).<sup>31</sup>

All three TMAs and two out of four thromboembolic events (TEs) were associated with the use of aPCC in HAVEN 1. Two TEs (acute myocardial infarction and occlusion of peripherally inserted central venous catheter) were reported on day 196 and were not associated with aPCC.<sup>31</sup> Four additional TEs occurred in postmarketing off-label use (three venous and one arterial) without aPCC or rFVIIa, but in patients suffering from acquired hemophilia. Until now, no TEs were reported in children.<sup>31</sup>

Altogether, approximately 7,500 PWHA were treated with emicizumab. Twenty-five (14 in HAVEN, 10 in STASEY, 1 outside of studies) developed immune reactions to emici-

zumab. The development of antidrug antibodies (ADAs) occurred in 3 of 398 participants (0.75%) enrolled in HAVEN clinical trials, and in one additional patient in the postmarketing use.<sup>35,36</sup> Notably, all four patients were children receiving Q4W prophylaxis.<sup>37</sup> Two of the reported children (6 and 13 years old with high-titer inhibitors, respectively) had a discontinued emicizumab treatment due to lack of efficacy. Both children showed a significantly elevated bleeding tendency as represented by a prolonged aPTT after approximately 2 to 3 months of emicizumab therapy.<sup>35,36</sup>

### Surgery

As mentioned earlier, emicizumab does change from a severe to a mild HA, but does not completely normalize hemostasis. Thus, additional replacement therapies have to be considered particularly for surgical interventions. The necessity, dose, and duration of replacing the factor (FVIII or BPA, respectively) should be adapted to the surgical procedure and postoperation course. Patients without inhibitors can be treated with FVIII substitutions as usual. By contrast, for patients with inhibitors, the first-line perioperative treatment is rFVIIa. In case of an inadequately efficient second-line treatment, recombinant porcine FVIII (not licensed) or aPCC (potential risk for TMA or thrombosis) are recommended. An initial dose of aPCC of greater than 50 U/kg BW should be avoided. Lower doses have been described to be effective and safe. If a perioperative treatment with aPCC is necessary for an elective major surgery, a withdrawal of emicizumab treatment could be considered for at least 6 months before surgery.<sup>38</sup>

For minor surgeries, additional treatment is not always necessary, but patients should be closely clinically monitored.<sup>38</sup>

### Previously Untreated Patients, Minimal Treated Patients, and Young Children (<2 Years)

Although emicizumab is approved for all age groups, data are limited for children. For this age group, only two studies (HAVEN 2: 88 children with inhibitors, and HOHEMI: 13 children without inhibitors), two larger real-world series (McCary et al: 93 PWHA with and without inhibitors; Barg et al: 40 PWHA with and without inhibitors), and some case reports or series with only a small number of children younger than 2 years are available.<sup>27,39–41</sup>

Children with inhibitors enrolled in HAVEN 2 showed a very low ABR of 0.3 in the QW group. Notably, in this group, 77% of patients had no bleeding events that required any medical interventions, and the intra-individual comparison of prophylaxis with BPA or emicizumab showed a reduction of the ABR by 99%. In the groups Q2W and Q4W, the ABR were 0.2 and 2.2, respectively. Altogether, only eight patients included in HAVEN 2 were younger than 2 years.<sup>27</sup>

In the HOHEMI trial, 13 Japanese children younger than 12 years were enrolled, and treated on a Q2W and Q4W schedule. Three participants were younger than 2 years, of whom one patient was a 3-month-old previously untreated

patient (PUP). The ABR of treated bleeding events was 1.4 and 0.7 in Q2W and Q4W, respectively, with 33 and 71% of patients without any bleedings.<sup>40</sup>

In the multicenter observational study of McCary et al, 19 children with inhibitors and 74 children without inhibitors ( $n = 93$ ) were enrolled. The median age was 8.6 years. The ABR decreased from 4.4 (patients with inhibitors) and 1.6 (patients without inhibitors) to 0.4 on emicizumab treatment. Of note, 10 patients without inhibitors were <2 years of age. This age group appears to have the highest benefit from emicizumab treatment, possibly due to a not completely established full prophylaxis regimen in this age group. The improvement is represented by a mean ABR of treated bleedings decreasing from 2 to 0.5. Similarly, the rate of no bleeding events increased from 42 to 83%. In the group of patients aged from 2 to 6 years, the ABR decreased from 1.5 to 0.3, with an increased rate of no bleedings (60–95%). A similar trend can be observed in the age group ranging from 6 to 12 years, with an ABR decreasing from 0.6 to 0.2, and a similarly increasing rate of no bleedings (82–94%).<sup>41</sup>

The earlier-mentioned report by Barg et al on the real-world experience included 18 children with inhibitors and 22 patients without inhibitors ( $n = 40$ ). Nine of the patients were infants (< 1 year), of whom eight displayed inhibitors. The ABR was 1 in both groups, and no bleeding events were reported in 44% of patients with inhibitors, and 55% of patients without inhibitors. All reported bleedings requiring treatment were trauma-related.<sup>39</sup> A later publication of Barg et al reported 18 more children, altogether now 58 pediatric patients (23 with and 35 without inhibitors), with a median treatment duration of 77 (41–92) weeks. As before, 29 (50%) children experienced zero bleeds. The majority of bleeds (94%) were traumatic bleedings with an increasing risk over duration of emicizumab prophylaxis. Unfortunately, one case of a fatal major bleeding occurred. A 5-month-old infant with a high-titer inhibitor, starting emicizumab in the age of 2.5 months, developed a large retroperitoneal hematoma after initiation of treatment with low-molecular-weight heparin because of a clot on tip of “central venous line (CVL)”. He died despite all treatment efforts.<sup>42</sup>

Collectively, all authors describe a good efficacy and safety in children younger than 12 years. However, these studies also show a particularly limited availability of data for young children (<2 years).

For PUPs or infants, only small case series or individual reports from single institutional experiences have been published. Mori et al reported approximately 12 children who were treated with emicizumab. Notably, in this cohort, three patients were PUPs (0–0.35 years old). Six patients in the age range of 0.6 to 1.8 years received on-demand treatment, and three children (2.9–10.7 years) received prophylaxis before being switched to emicizumab treatment regimens. A median observation time of 49 weeks (19–139) was described. In PUPs, the ABR was 0 before and 0.9 (0–3.2) on emicizumab, respectively. By contrast, in the on-demand group, the ABR was 4.6 before and 1.9 on emicizumab treatment. Emicizumab has been reported to be safe and effective. Parents’ opinions were reported as follows: re-

duced anxiety about bleeding (e.g., able to travel without worrying about bleedings), reduced stress from injections, reduced frequency of emergency room visits due to injection failure, and being able to entrust a child to nursery school at a younger age. However, parents do report about anxiety on whether or not sports can be done safely while being on emicizumab prophylaxis.<sup>43</sup> Bush et al described the course of six young children from San Diego: three very young boys were in the age range of 1 to 6 months (one PUP: 1 month old; 2 minimal treated patients [MTPs]: 1 month old: 3 exposure days (ED); 6 month old: 15 ED), two children were 10 to 13 months old (MTPs: 10 months: 1 ED; 13 months: 11 ED), and one child was 23 months old when starting emicizumab treatment. The youngest patients received 0 to 7 FVIII substitutions in addition to emicizumab, which were not bleeding related. Two children in the middle age group received 4 to 11 FVIII substitutions, but developed an inhibitor while being on emicizumab. The oldest boy was treated with emicizumab because of an inhibitor, and did not receive any additional substitutions. Consequently, the authors highlighted the importance of inhibitor monitoring following FVIII substitutions on emicizumab.<sup>44</sup>

Heine and Graf reported approximately nine patients without inhibitors who were aged 0.5 to 14 years, and treated with emicizumab. Two of them were PUPs (6 and 22 months). Only two patients needed additional FVIII substitutions once or twice. Patients’ and caregivers’ satisfaction was reported to be high.<sup>45</sup>

In PWA, it is recommended to start prophylaxis as soon as possible, ideally within the first 2 years of life and before the first joint bleed.<sup>1,2</sup> The frequent intravenous injections are the largest burden of prophylaxis, especially in very small children due to the requirement of a CVAD. Thus, the benefit of bleeding prevention has to be balanced against the need and risks of a CVAD implementation.<sup>2</sup> Therefore, the median age for initiating CFC prophylaxis was 1.3 years in the PedNet cohort.<sup>2,46</sup> Prophylaxis is often started with a once weekly schedule because of poor vein access and also to prevent inhibitor development. However, this schedule does not achieve full prevention of bleedings.<sup>2,4</sup>

In the group of infants and PUPs, which particularly often displays unmet needs, emicizumab could be an attractive and promising treatment option due to the subcutaneous administration. However, for this subgroup of patients, we have only a very limited availability of data. Additionally, we have some unanswered questions that need to be addressed in the context of emicizumab use in young children. For instance, what about the pharmacokinetics of emicizumab in newborn and very young infants? This drug binds to FIXa and FX, both of which are factors that are comparatively low in newborn. Of note, in a mouse model the efficacy of emicizumab was significantly altered when human FIX and FX levels were low.<sup>26</sup> Thus, the question about the potency of emicizumab in newborn and very young infants is immediately arising.<sup>47</sup>

Emicizumab changes a severe HA to a mild HA. However, reaching 50 ED in young patients could easily take up to 13 to 20 years.<sup>1,48</sup> Thus, an immediately upcoming question is of

course whether an inhibitor development is just postponed to a later point in life. It is known that the risk of an inhibitor development is higher in on-demand treatment schedules due to an associated higher dose of factor substitution in the context of major bleeding events. Thus, if the only option is to substitute factor in the case of bleedings or surgeries, will the inhibitor risk increase? Can we achieve tolerance with additional low-dose FVIII substitutions that are given weekly or biweekly?

To answer these questions, more in-depth studies are required. Some of these are already ongoing (►Table 1). However, the acquisition of solid and finalized data will take several years. In the meantime, patients, caregivers, and physicians will have an increasing demand of emicizumab. This is the reason why some experts and expert groups gave some recommendations for the use of emicizumab, and discussed advantages as well as disadvantages of the treatment regimens.<sup>1,37,38,48</sup> The publications by a European group of experts<sup>1</sup> and by Young,<sup>48</sup> a U.S. expert in treatment of children, should be particularly emphasized here.

Current standard of care is simply a replacement of what is missing, thus substituting FVIII.<sup>1,38,48</sup> While the European expert group seems more hesitant about the use in very young children, Guy Young suggests different algorithms in order to make treatment decisions in children.<sup>1,48</sup> Despite the differences in approaching treatment regimens in young children, both do agree on the fact that the treatment of very young children is best suited in the setting of studies, or well-managed registries (e.g., GEPHARD [www.gephard.de; e-mail: info@gephard.de], PedNet). In addition, emicizumab should be started in comprehensive care centers with sufficient clinical and laboratory experience.<sup>1,37,38</sup> The treatment of newborn or infants should be a case-by-case decision.<sup>1,48</sup>

Particularly in the context of preventing ICH, Guy Young strongly recommends to discuss the option of an early emicizumab prophylaxis with parents of all newly diagnosed severe HA patients.<sup>48</sup>

Importantly, decisions about any prophylaxis regimen should be made with parents and caregivers in an informed, shared decision-making process, which takes into account several advantages and disadvantages: efficacy (early protection against ICH, achieving life-long joint protection, achieving tolerance to FVIII), safety (less experience with emicizumab, risk for inhibitor development, lack of natural antagonists for emicizumab), and practical considerations (vein access).<sup>1</sup>

### Suggested Algorithm by Young

If you have a new patient (PUP) with severe HA younger than 9 months with the strong desire or need to start prophylaxis, especially due to ICH risk, there is the option to start emicizumab with the earlier discussed limitations (for instance delayed/increased inhibitor development).<sup>48</sup>

The next decision point for these children is when they are around 9 months old and revolve around initiation of FVIII prophylaxis, because major limitation of emicizumab mono-

therapy is a possibly delayed inhibitor development. At this point, one could consider substituting FVIII weekly or biweekly to achieve immune tolerance. However, for this approach, no data are available. Additionally, it is unknown whether weekly or biweekly schedules are sufficient to prevent inhibitor development.

For PUPs older than 9 months, it can be considered to start the standard-of-care/traditional approach with FVIII replacement, or emicizumab initiation as a new option. Starting emicizumab in this age group would lead to the same limitations with a potential delayed and/or increased inhibitor risk, raising the question whether adding FVIII for at least 50 EDs can be beneficial to achieve tolerance, and to unmask inhibitors.

Patients receiving FVIII prophylaxis and reaching >50 ED without inhibitor development could then decide whether to continue with FVIII prophylaxis, or to switch to emicizumab.<sup>48</sup>

### Older Patients/Previously Treated Patients

The older the patients, the more data are available from the HAVEN 1–4 trials concerning efficacy and safety. Emicizumab prophylaxis resulted in a markedly lower ABR, and over the time ABR seems to decline with a mean treated ABR of 0.7 at week 121 to 144 ( $n = 170$ ).<sup>28,30,31,34</sup>

As reported earlier, in the HOHEMI trial, and in the multicenter observational study of McCary, the efficacy of emicizumab was shown to be very good with a low ABR.<sup>40,41</sup> All caregivers in the HOHEMI study completed the preference survey after the first 16 weeks of treatment, and all reported a preference of emicizumab prophylaxis over the patient's previous HA treatment. Reasons influencing their preference were as follows: “the frequency of treatments was lower” and “route of administration was easier.” Another important point was: “effect on other activities (work, school, sports, and social interactions) was less” (from 3/13 caregivers, 23.1%).<sup>40</sup>

However, data for long-term outcome are still missing. The longest reported observation time is around 3 years in HAVEN 1–4 and 5.8 years in the phase 1 and 1/2 dose finding study.<sup>31,32</sup>

Additionally, it is regularly discussed how important peak levels are for long-term outcome. Is emicizumab prophylaxis sufficient for high activity sports to prevent bleedings, or do we need peak levels? What about the functions of FVIII outside of coagulation, for instance, with regard to bone health?<sup>37,48</sup>

### Suggested Algorithm by Young

Young suggested a decision-making process based on response (quantity of bleedings), adherence, and satisfaction. Thus, patients doing well without bleedings, and are adherent and satisfied with current FVIII therapy, should continue without further adjustment.

Patients who are not responding, adherent and/or satisfied, and currently on SHL FVIII could then switch to an EHL. Alternatively, emicizumab would be a possible regimen in these patients.<sup>48</sup>

**Table 1** Remaining questions and associated clinical trials

Question	Title	ClinicalTrials.gov Identifier	Description
<ul style="list-style-type: none"> <li>• When shall we start emicizumab prophylaxis? What about PUPs and infants?</li> <li>• What about long-term safety?</li> </ul>			
PUPs and infants (≤12 mo)	A Study to Evaluate the Efficacy, Safety, Pharmacokinetics, and Pharmacodynamics of Subcutaneous Emicizumab in Participants from Birth to 12 Months of Age with Hemophilia A without Inhibitors (HAVEN 7)	NCT04431726	Phase IIIb, multicenter, open-label, single-arm study of prophylactic emicizumab in PUPs and MTPs from birth to ≤12 mo of age with severe HA without FVIII inhibitors. After 1 y: continue emicizumab over a 7-y long-term follow-up
<ul style="list-style-type: none"> <li>• Should we do low-dose FVIII substitution on emicizumab in PUPs and MTPs?</li> <li>• Is Inhibitor development postponed “until later”?</li> <li>• Will the inhibitor risk increase due to big treatment moments?</li> </ul>			
Inhibitor prevention (FVIII + Emicizumab)	The Hemophilia Inhibitor Prevention Trial	NCT04303559	Multicenter, randomized phase III clinical trial, Eloctate vs. emicizumab, using adaptive design, to prevent inhibitors in patients with severe HA
Inhibitor prevention (FVIII + Emicizumab) and ITI	Emicizumab PUPs and Nuwiq ITI Study	NCT04030052	Prospective study: safety, FVIII immunogenicity, hemostatic efficacy of HEMLIBRA with a concomitant low-dose rFVIII (NUWIQ), in children <3 y (PUPs and MTPs). And investigation of safety and efficacy of a novel FVIII ITI regimen in children with low- and high-titer inhibitors
<ul style="list-style-type: none"> <li>• What is the role of ITI in patients with newly developed inhibitors while emicizumab treatment?</li> <li>• Shall we do a high-dose or low-dose ITI regimens while on emicizumab prophylaxis</li> </ul>			
ITI	Treatment of Hemophilia A Patients with FVIII Inhibitors (MOTIVATE)	NCT04023019	Noninterventional, multicenter, observational, international study. Current ITI approaches: evaluating efficacy and safety of ITI, including the combination of FVIII and emicizumab
	The Hemophilia Inhibitor Eradication Trial	NCT04303572	Multicenter randomized phase III clinical trial, Eloctate ITI plus emicizumab vs. Eloctate ITI alone to eradicate inhibitors in severe HA
<ul style="list-style-type: none"> <li>• Durability of immune tolerance post-ITI after switching to emicizumab monotherapy</li> </ul>			
Inhibitor recurrence post-ITI	Preventing Inhibitor Recurrence Indefinitely (PRIORITY)	NCT04621916	Randomized, controlled 2-arm study, randomization of patients post-successful ITI to emicizumab plus weekly FVIII vs. emicizumab alone
<ul style="list-style-type: none"> <li>• Do we need FVIII peak levels for (high activity) sports?</li> </ul>			
Playing sports	Prevention of Bleeding in Patients with Moderate and Severe Hemophilia A Playing Sports: A Comparison between Factor VIII and Emicizumab Prophylaxis (STEP)	NCT05022459	Emicizumab vs. FVIII to prevent bleeding in PWA who play sports. Children and adolescents, receiving already emicizumab or FVIII who playing sports
<ul style="list-style-type: none"> <li>• Do we need FVIII for bone health?</li> </ul>			
Joint and bone health	Effects of Emicizumab versus Factor VIII Prophylaxis on Joint and Bone Health in Severe Hemophilia A (EmiMSK)	NCT04131036	Longitudinally assessment of joint health and bone density over 3 y. Comparison of effect of routine FVIII vs. emicizumab in PWA

(Continued)

**Table 1** (Continued)

Question	Title	ClinicalTrials.gov Identifier	Description
	POCUS: Hemostatic Potential and Joint Health in Patients With Severe Hemophilia A on Novel Replacement Therapies	NCT04690322	Prospective, randomized control trial, randomization: EHL FVIII therapy vs. NFT (emicizumab)
<b>• What about safety of aPCC?</b>			
aPCC use	SAFE Study: Safety of aPCC Following Emicizumab Prophylaxis (SAFE)	NCT04563520	Prospective study, safety, and hemostatic efficacy of a personalized dose of aPCC in PWHA and inhibitors on emicizumab during acute bleedings or prior to procedures
	A Study to Evaluate the Safest Dose Range for FEIBA in Hemophilia A Patients With Inhibitors on Emicizumab	NCT04205175	Study of in vivo combination of Feiba in patients with inhibitors on emicizumab

Abbreviations: aPCC, activated prothrombin complex concentrate; EHL, extended half-life products; HA, hemophilia A; ITI, immune tolerance induction; MTPs, minimal treated patients; Non-factor therapy (NFT); PUPs, previously untreated patients; PWHA, patients with hemophilia A.

## Patients with Inhibitors

In the HAVEN 1 and 2 trials, the superiority of emicizumab treatment in HA patients with inhibitors was clearly demonstrated.<sup>27,30</sup> As reported earlier, children with inhibitors enrolled in HAVEN 2 showed a very low ABR, with the majority of patients requiring no bleeding-related treatments. The intraindividual comparison of prophylaxis with BPA or emicizumab showed a reduction of the ABR by 99%.<sup>49</sup> Thus, experts recommend starting emicizumab as a bleeding prophylaxis for PWHA with inhibitors that have not started ITI yet, or that have started ITI but did not completely clear their antibodies. This implies that emicizumab should be prescribed independently from ITI.<sup>27,48,50</sup>

Due to thromboses and TMAs observed in emicizumab-treated patients receiving high-dose aPCC for the management of bleeding events, therapy with rFVIIa is recommended instead.<sup>38</sup>

Despite a high efficacy of emicizumab in patients with inhibitors, it is still strongly recommended to perform at least one ITI to achieve tolerance to FVIII, to account for patients' safety (higher mortality in inhibitor patients, better treatment options with FVIII during surgery or bleedings). Additionally, it needs to be considered that currently the eligibility criteria for potential gene therapy trials are met only when no inhibitors are present, thus providing a rationale for superiority of an ITI attempt.<sup>27,28,48–52</sup> It is the topic of current discussions when and how ITI regimens should be performed. Generally, there are two dose schedules: the high-dose schedule (HD; also known as the modified Bonn protocol) with 200 IE/kg BW FVIII per day and the low-dose (LD) schedule with 50 IE/kg BW FVIII per day.

The International Immune Tolerance Study compared these two schedules as a randomized, multicenter, prospective trial. Patients with good-risk profile (peak inhibitor >5 and <200 BU; start inhibitor titer <10 BU before randomi-

zation, titer decline to <10 BU in <12 months) were included. Patients with peak inhibitors >200 BU were excluded. The outcome of patients did not differ between treatment arms, but the time until achieving a negative titer, a normal recovery, and immune tolerance were shorter in the HD-ITI arm. Participants in LD-ITI arm had more bleeding events than patients in the HD-ITI arm, leading to a preponed stop of the trial due to concerns about patients' safety.<sup>24</sup>

Although most experts agree to start emicizumab in patients with newly diagnosed high-titer inhibitors in addition to an ITI, the specific ITI regimen (LD vs. HD-ITI) is still controversially discussed.

Arguments for the LD-ITI arm are a higher efficacy in preventing bleeding episodes while emicizumab treatment when compared with BPA prophylaxis, as well as a subsequent reduction of CVAD implementations and their related complications, such as infection and thrombosis. Whether low-dose ITI combined with emicizumab prophylaxis is economically more efficient than high-dose ITI remains to be elucidated.<sup>28,37,49–51</sup>

Experts, such as Young and Le Quellec and Negrier, would generally recommend the LD-ITI while emicizumab treatment.<sup>28,49,50</sup> This is due to a comparable final efficacy of LD-ITI versus HD-ITI in the International ITI study. The observed higher bleeding rate in the LD-ITI arm is then overcome by the use of emicizumab as an efficient treatment option. Based on the same argument, the FIT group (international experts) is recommending to start with a low-dose ITI (50 IE/kg BW 3 times per week), combined with emicizumab in patients with good (max. pre-ITI inhibitor 25–199 BU) and very good prognosis (<25 BU). In case of increasing inhibitor titers, the group is recommending to change the ITI regimen to a dose of 200 IU/kg BW daily. By contrast, the FIT group suggests an HD-ITI for patients with poor prognosis (pre-ITI inhibitor >200 BU) and very poor prognosis (>1,000 BU). However, the German expert panel is already recommending

an HD-ITI regimen if the inhibitor titer is greater than 50 BU (Bethesda Unit).<sup>52</sup>

To better address these discussed points, the so-called Atlanta protocol included patients with QW or Q2W emicizumab schedules together with a LD-ITI regimen (FVIII 50–100 IE/kg BW 3 times per week), whose first interim results were published.<sup>53</sup> Enrolled were seven patients with pre-ITI inhibitors (four high-titer and three low-titer patients, of whom one patient had a high titer before decreasing to a low titer). Five of these patients had prior ITI attempts. During a median observation time of 35 weeks (21–40 weeks), inhibitor titers decreased in all patients. Three patients became negative for inhibitors, of whom two patients displayed recovery rates of greater than 66%, and the third patient had a recovery rate of 64%. Half-life of FVIII was not applicable in these patients. Thus, the published data clearly demonstrate that LD-ITI is indeed feasible while emicizumab treatment.<sup>53</sup>

### Post-ITI

Another important aspect that is currently under discussion involves the post-ITI procedure. Patients who failed ITI could stay on, or start with emicizumab.<sup>48</sup>

However, the more difficult question is how to manage the patients after successful ITI.<sup>51,52</sup> Thus, the key question is whether FVIII is needed to maintain immune tolerance. To answer this question, the PRIORITY study was initiated (–Table 1).

In a multicenter retrospective cohort study, a recurrence rate of approximately 30% was described independently from adherence to post-ITI FVIII prophylaxis or not. This means that in both groups (with or without FVIII prophylaxis), 29% of patients relapsed.<sup>25</sup>

In this context, the German expert panel discussed three options: (1) ongoing prophylaxis with emicizumab after FVIII is gradually withdrawn; (2) ongoing prophylaxis with emicizumab in addition to low-frequency FVIII substitutions to maintain tolerance; (3) discontinuation of emicizumab prophylaxis, and instead switching to prophylaxis with FVIII exclusively (traditional approach).<sup>52</sup> Concerning the second option, there is only little evidence on the ideal dosing regimen for FVIII. For option 1, all experts suggest a slow withdrawal of FVIII.<sup>51,52</sup> The FIT-group recommended maintaining patients on a minimum of weekly FVIII infusions for at least 6 months, followed by additional 6 months of biweekly dosing. During this time, testing for neutralizing (and where possible non-neutralizing) anti-FVIII antibodies should be performed every 1 to 2 months, alongside recovery testing every 2 to 4 months. After this, regular exposure to FVIII can be discontinued with ongoing surveillance for anti-FVIII antibody development, and FVIII pharmacokinetic studies (every 3–6 months).<sup>51</sup>

Batsuli et al published a single-institution retrospective review of 12 pediatric patients receiving emicizumab, followed by successful ( $n = 7$ ) or partially successful ( $n = 5$ ) ITI. Duration of post-ITI FVIII substitution varied between 0.2 and 11 years. Three patients were treated with FVIII in addition to emicizumab (twice weekly, once weekly, or

biweekly). Of these 12 patients, 1 child displayed only a partial response to ITI, followed by a 1.3-year-period of post-ITI FVIII prophylaxis before being switched to emicizumab only. Unfortunately, this patient relapsed on this regimen. Six patients (2/7 after successful ITI, and 4/5 with partial response) in this study became IgG4 positive without displaying an IgG1 positivity. Of note, one of these IgG4-positive patients was the earlier-mentioned child relapsing on emicizumab only. Interestingly, there was no inhibitor recurrence after re-exposure to FVIII in the context of bleeding or surgery-associated events. An ongoing inhibitor monitoring in post-ITI patients receiving emicizumab is strongly recommended.<sup>54</sup>

### Remaining Important Questions and Clinical Trials

As mentioned earlier, some crucial questions are remaining with regard to the use of emicizumab. Some of them are being addressed in clinical trials (–Table 1).

### Conclusion

Emicizumab is the first approved NRT for bleeding prophylaxis in PWHAs in the presence of inhibitors, as well as in patients with severe HA without inhibitors, and is administered subcutaneously. Clinical trials and real-world observational studies could demonstrate a good efficacy and safety for bleeding prevention with emicizumab in PWHAs with and without inhibitors, indicating a potential improvement in HA management. Especially in PWHAs with inhibitors, emicizumab is on the way to become standard of care. However, there are some crucial questions remaining and missing data, especially concerning young children and PUPs, ITI and post-ITI procedure regimens, long-term safety, bone health, and bleeding prevention in the context of high activity sports. Some of these questions are being addressed in clinical trials. To avoid missing crucial information and experiences, all data of treated HA patients should be collected in registries or clinical studies. Until generation of finalized and reliable data answering the earlier-mentioned questions, the recommendations of experts and expert groups are of pivotal importance to achieve the best standard of care for all PWHAs.

### Conflict of Interest

Research funding: CSL Behring; clinical trials/studies: Boehringer-Ingelheim, Pfizer, Roche/Chugai, Shire, Sobi; consultation: Bayer, Biotest, CSL Behring, Novo Nordisk, Octapharma, Pfizer, Roche/Chugai, Shire/Takeda, and Sobi.

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## References

- Mancuso ME, Male C, Kenet G, et al. Prophylaxis in children with haemophilia in an evolving treatment landscape. *Haemophilia* 2021;27(06):889–896
- Fischer K, Collins PW, Ozelo MC, Srivastava A, Young G, Blanchette VS. When and how to start prophylaxis in boys with severe hemophilia without inhibitors: communication from the SSC of the ISTH. *J Thromb Haemost* 2016;14(05):1105–1109
- World Federation of Hemophilia. World Bleeding Disorders Registry. Data Report 2020. <https://www1.wfh.org/publications/files/pdf-1971.pdf>
- Kurnik K, Bidlingmaier C, Engl W, Chehadeh H, Reipert B, Auerswald G. New early prophylaxis regimen that avoids immunological danger signals can reduce FVIII inhibitor development. *Haemophilia* 2010;16(02):256–262
- Andersson NG, Auerswald G, Barnes C, et al. Intracranial haemorrhage in children and adolescents with severe haemophilia A or B - the impact of prophylactic treatment. *Br J Haematol* 2017;179(02):298–307
- Chalmers EA, Alamelu J, Collins PW, et al; Paediatric & Rare Disorders Working Parties of the UK Haemophilia Doctors Organization. Intracranial haemorrhage in children with inherited bleeding disorders in the UK 2003–2015: a national cohort study. *Haemophilia* 2018;24(04):641–647
- Zanon E, Pasca S. Intracranial haemorrhage in children and adults with haemophilia A and B: a literature review of the last 20 years. *Blood Transfus* 2019;17(05):378–384
- Witmer C, Presley R, Kulkarni R, Soucie JM, Manno CS, Raffini L. Associations between intracranial haemorrhage and prescribed prophylaxis in a large cohort of haemophilia patients in the United States. *Br J Haematol* 2011;152(02):211–216
- Warren BB, Thornhill D, Stein J, et al. Young adult outcomes of childhood prophylaxis for severe hemophilia A: results of the Joint Outcome Continuation Study. *Blood Adv* 2020;4(11):2451–2459
- Oldenburg J. Optimal treatment strategies for hemophilia: achievements and limitations of current prophylactic regimens. *Blood* 2015;125(13):2038–2044
- Srivastava A, Santagostino E, Dougall A, et al; WFH Guidelines for the Management of Hemophilia panelists and co-authors. WFH guidelines for the management of hemophilia, 3rd edition. *Haemophilia* 2020;26(Suppl 6):1–158
- Querschnitts-Leitlinie (BÄK) zur Therapie mit Blutkomponenten und Plasmaderivaten. Gesamtnovelle 2020. <https://www.baek.de/qll-haemotherapie-2020>
- DiMichele D. The North American Immune Tolerance Registry: contributions to the thirty-year experience with immune tolerance therapy. *Haemophilia* 2009;15(01):320–328
- Gouw SC, van der Bom JG, Marijke van den Berg H. Treatment-related risk factors of inhibitor development in previously untreated patients with hemophilia A: the CANAL Cohort study. *Blood* 2007;109(11):4648–4654
- van den Berg HM, Fischer K, Carcao M, et al; PedNet Study Group. Timing of inhibitor development in more than 1000 previously untreated patients with severe hemophilia A. *Blood* 2019;134(03):317–320
- Peyvandi F, Mannucci PM, Garagiola I, et al. A randomized trial of factor VIII and neutralizing antibodies in hemophilia A. *N Engl J Med* 2016;374(21):2054–2064
- Abshire T, Kenet G. Recombinant factor VIIa: review of efficacy, dosing regimens and safety in patients with congenital and acquired factor VIII or IX inhibitors. *J Thromb Haemost* 2004;2(06):899–909
- Schneiderman J, Rubin E, Nugent DJ, Young G. Sequential therapy with activated prothrombin complex concentrates and recombinant FVIIa in patients with severe haemophilia and inhibitors: update of our previous experience. *Haemophilia* 2007;13(03):244–248
- Astermark J, Donfield SM, DiMichele DM, et al; FENOC Study Group. A randomized comparison of bypassing agents in hemophilia complicated by an inhibitor: the FEIBA NovoSeven Comparative (FENOC) Study. *Blood* 2007;109(02):546–551
- Konkle BA, Ebbesen LS, Erhardtsen E, et al. Randomized, prospective clinical trial of recombinant factor VIIa for secondary prophylaxis in hemophilia patients with inhibitors. *J Thromb Haemost* 2007;5(09):1904–1913
- Leissinger C, Gringeri A, Antmen B, et al. Anti-inhibitor coagulant complex prophylaxis in hemophilia with inhibitors. *N Engl J Med* 2011;365(18):1684–1692
- Oldenburg J, Austin SK, Kessler CM. ITI choice for the optimal management of inhibitor patients - from a clinical and pharmacoeconomic perspective. *Haemophilia* 2014;20(Suppl 6):17–26
- Jiménez-Yuste V, Oldenburg J, Rangarajan S, Peiró-Jordán R, Santagostino E. Long-term outcome of haemophilia A patients after successful immune tolerance induction therapy using a single plasma-derived FVIII/VWF product: the long-term ITI study. *Haemophilia* 2016;22(06):859–865
- Hay CR, DiMichele DM International Immune Tolerance Study. The principal results of the International Immune Tolerance Study: a randomized dose comparison. *Blood* 2012;119(06):1335–1344
- Antun A, Monahan PE, Manco-Johnson MJ, et al. Inhibitor recurrence after immune tolerance induction: a multicenter retrospective cohort study. *J Thromb Haemost* 2015;13(11):1980–1988
- Ferrière S, Peyron I, Christophe OD, et al. A hemophilia A mouse model for the in vivo assessment of emicizumab function. *Blood* 2020;136(06):740–748
- Young G, Liesner R, Chang T, et al. A multicenter, open-label phase 3 study of emicizumab prophylaxis in children with hemophilia A with inhibitors. *Blood* 2019;134(24):2127–2138
- Young G. How I treat children with haemophilia and inhibitors. *Br J Haematol* 2019;186(03):400–408
- 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(09):811–822
- Oldenburg J, Mahlangu JN, Kim B, et al. Emicizumab prophylaxis in hemophilia A with inhibitors. *N Engl J Med* 2017;377(09):809–818
- Callaghan MU, Negrier C, Paz-Priel I, et al. Long-term outcomes with emicizumab prophylaxis for hemophilia A with or without FVIII inhibitors from the HAVEN 1–4 studies. *Blood* 2021;137(16):2231–2242
- Shima M, Nagao A, Taki M, et al. Long-term safety and efficacy of emicizumab for up to 5.8 years and patients' perceptions of symptoms and daily life: a phase 1/2 study in patients with severe haemophilia A. *Haemophilia* 2021;27(01):81–89
- 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(09):1384–1393
- Pipe SW, Shima M, Lehle M, et al. Efficacy, safety, and pharmacokinetics of emicizumab prophylaxis given every 4 weeks in people with haemophilia A (HAVEN 4): a multicentre, open-label, non-randomised phase 3 study. *Lancet Haematol* 2019;6(06):e295–e305
- Harkins Druzgal C, 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;18(09):2205–2208
- Valsecchi C, Gobbi M, Beeg M, et al. Characterization of the neutralizing anti-emicizumab antibody in a patient with hemophilia A and inhibitor. *J Thromb Haemost* 2021;19(03):711–718
- Le Quellec S. Clinical evidence and safety profile of emicizumab for the management of children with hemophilia A. *Drug Des Devel Ther* 2020;14:469–481

- 38 Holstein K, Albisetti M, Bidlingmaier C, et al; 'Ständige Kommission Hämophilie' (Haemophilia board) of the German, Swiss Austrian Society for Thrombosis Haemostasis Research (GTH) Practical guidance of the GTH Haemophilia Board on the use of emicizumab in patients with haemophilia A. *Hamostaseologie* 2020;40(05):561–571
- 39 Barg AA, Livnat T, Budnik I, et al. Emicizumab treatment and monitoring in a paediatric cohort: real-world data. *Br J Haematol* 2020;191(02):282–290
- 40 Shima M, Nogami K, Nagami S, et al. A multicentre, open-label study of emicizumab given every 2 or 4 weeks in children with severe haemophilia A without inhibitors. *Haemophilia* 2019;25(06):979–987
- 41 McCary I, Guelcher C, Kuhn J, et al. Real-world use of emicizumab in patients with haemophilia A: bleeding outcomes and surgical procedures. *Haemophilia* 2020;26(04):631–636
- 42 Barg AA, Budnik I, Avishai E, et al. Emicizumab prophylaxis: prospective longitudinal real-world follow-up and monitoring. *Haemophilia* 2021;27(03):383–391
- 43 Mori MNC, Umezawa Y, Sudo A, Ashikaga T, Yamashita A, Taki M. emicizumab treatment in pediatric patients with hemophilia A without inhibitors: a single-institution study. *Res Pract Thromb Haemost* 2020;4(Suppl 1):2020
- 44 Bush KA, Ding H, O'Flaherty-Keese K, et al. Real-world clinical outcomes in previously untreated and minimally treated patients with congenital factor VIII deficiency: the San Diego experience. *Blood* 2020;136:31–32
- 45 Heine SI, Graf N. Real life use of emicizumab in pediatric patients without inhibitors. [abstract] *Res Pract Thromb Haemost* 2020;4(Suppl 1):2020
- 46 Nijdam A, Altisent C, Carcao MD, et al; PedNet and CANAL Study Groups. Bleeding before prophylaxis in severe hemophilia: paradigm shift over two decades. *Haematologica* 2015;100(03):e84–e86
- 47 Andrew M, Paes B, Milner R, et al. Development of the human coagulation system in the healthy premature infant. *Blood* 1988;72(05):1651–1657
- 48 Young G. Management of children with hemophilia A: how emicizumab has changed the landscape. *J Thromb Haemost* 2021;19(07):1629–1637
- 49 Young G. Implementing emicizumab in hemophilia inhibitor management: emicizumab should be prescribed after tolerance. *Blood Adv* 2018;2(20):2780–2782
- 50 Le Quellec S, Negrier C. Emicizumab should be prescribed independent of immune tolerance induction. *Blood Adv* 2018;2(20):2783–2786
- 51 Carcao M, Escuriola-Ettingshausen C, Santagostino E, et al; Future of Immunotolerance Treatment Group. The changing face of immune tolerance induction in haemophilia A with the advent of emicizumab. *Haemophilia* 2019;25(04):676–684
- 52 Escuriola-Ettingshausen C, Auerswald G, Königs C, et al. Optimizing the management of patients with haemophilia A and inhibitors in the era of emicizumab: recommendations from a German expert panel. *Haemophilia* 2021;27(03):e305–e313
- 53 Batsuli G, Zimowski KL, Tickle K, Meeks SL, Sidonio RF Jr. Immune tolerance induction in paediatric patients with haemophilia A and inhibitors receiving emicizumab prophylaxis. *Haemophilia* 2019;25(05):789–796
- 54 Batsuli G, Greene A, Meeks SL, Sidonio RF Jr. Emicizumab in tolerized patients with hemophilia A with inhibitors: a single-institution pediatric cohort assessing inhibitor status. *Res Pract Thromb Haemost* 2021;5(02):342–348