Emicizumab for the Treatment of Acquired Hemophilia A: Consensus Recommendations from the GTH-AHA Working Group

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Abstract

Background Acquired hemophilia A (AHA) is a severe bleeding disorder caused by autoantibodies against coagulation factor VIII (FVIII). Standard treatment consists of bleeding control with bypassing agents and immunosuppressive therapy. Emicizumab is a bispecific antibody that mimics the function of activated FVIII irrespective of the presence of neutralizing antibodies. Recently, the GTH-AHA-EMI study demonstrated that emicizumab prevents bleeds and allows to postpone immunosuppression, which may influence future treatment strategies.

Aim To provide clinical practice recommendations on the use of emicizumab in AHA.

Methods A Delphi procedure was conducted among 33 experts from 16 German and Austrian hemophilia care centers. Statements were scored on a scale of 1 to 9, and agreement was defined as a score of $\geq$7. Consensus was defined as $\geq$75% agreement among participants, and strong consensus as $\geq$95% agreement.

Results Strong consensus was reached that emicizumab is effective for bleed prophylaxis and should be considered from the time of diagnosis (100% consensus). A fast-loading regimen of 6 mg/kg on day 1 and 3 mg/kg on day 2 should be used if rapid bleeding prophylaxis is required (94%). Maintenance doses of 1.5 mg/kg once weekly should be given (91%). Immunosuppression should be offered to patients on

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emicizumab if they are eligible based on physical status (97%). Emicizumab should be discontinued when remission of AHA is achieved (97%).

Conclusion These GTH consensus recommendations provide guidance to physicians on the use of emicizumab in AHA and follow the results of clinical trials that have shown emicizumab is effective in preventing bleeding in AHA.

Introduction

Acquired hemophilia A (AHA) is a rare and potentially life-threatening bleeding disorder caused by autoantibodies against coagulation factor VIII (FVIII). Standard treatment of AHA is to control bleeding with agents bypassing or replacing human FVIII such as recombinant factor VIIa (rFVIIa), activated prothrombin complex concentrate (aPCC), and recombinant porcine factor VIII (rpVIII, susoctocog alfa).[1] These agents are effective for bleed control,[2–4] but application is burdensome due to their short half-life and the need for frequent intravenous injections.[5] In addition, bleeding risk remains high, even after successful treatment of a first bleed.[2] Next to the treatment of bleeding, immunosuppressive agents like steroids, cyclophosphamide, and rituximab are used for the eradication of the inhibitory antibodies. However, intensive immunosuppressive therapy (IST) in AHA is associated with a high mortality related to infectious complications.[6–8]

Emicizumab is a bispecific antibody that bridges activated coagulation factor IX with factor X promoting amplification and propagation of thrombin generation after activation of the coagulation cascade in the absence of FVIII. Emicizumab is licensed for the treatment of inherited hemophilia A with inhibitory antibodies and for severe hemophilia A without inhibitors and was recently licensed for patients with moderate hemophilia A and severe bleeding phenotype.[9–11] Use of emicizumab in AHA is off-label in most parts of the world, including Europe and the United States, but it was recently approved for AHA in Japan. It was reported in several case reports,[12] a series from Vienna ($n = 12$),[13] a clinical trial from Japan (AGEHA, $n = 11$),[14] and the GTH-AHA-EMI trial ($n = 47$).[15] An ongoing trial in the United States (AHAEmi, NCT05345197) is evaluating emicizumab in patients in whom immunosuppression can be given at the discretion of the investigators. The AGEHA-, the GTH-AHA-EMI, and the AHAEmi trials use an accelerated emicizumab loading regimen of 6 mg/kg (day 1) and 3 mg/kg (day 2), followed by 1.5 mg/kg once weekly. In the GTH-AHA-EMI trial, efficacy was studied for 12 weeks while patients did not receive immunosuppression. The study achieved its primary endpoint with a mean bleeding rate of 0.04 bleed per patient-week. Only two thrombotic events occurred, and the overall survival was 91%.[15]

The efficacy of emicizumab for bleeding prophylaxis has the potential to change clinical practice of AHA management. In addition to preventing bleeding, it may also allow early hospital discharge, outpatient management, and deferral of IST in critically ill patients. Here, members of the GTH-AHA working group employed a structured Delphi procedure to generate consensus statements on important aspects of the routine clinical use of emicizumab in AHA.

Methods

A Delphi consensus procedure was conducted to establish consensus recommendation. All 51 physicians who were involved in the GTH-AHA-study were asked for participation. Members of the GTH-AHA study group were selected for the Delphi consensus process, because all were familiar with the treatment of AHA and the results of the GTH-AHA study were known before publication. Of those 51 physicians, 14 agreed to participate in a steering committee to develop the statements and evaluate the responses in the Delphi process.

A list of 12 statements was generated by the steering committee and sent to all 51 physicians involved in the GTH-AHA study. The clinicians were asked to express their agreement/disagreement on a scale of 1 (strongly disagree) to 9 (strongly agree). Agreement was defined as a score ≥ 7. Participants were asked to provide explanations in case of disagreement (score ≤ 6). Consensus was defined as $\geq 75\%$ agreement and strong consensus as $\geq 95\%$ agreement. A total of 33 clinicians responded.

After one round, strong consensus was achieved in seven, consensus in four, and no consensus in one statement. The responses and comments were evaluated by the steering committee. Due to the high level of consensus and the clear comments from the participants, the steering committee decided not to hold another Delphi round.

Consensus Statements

General Considerations

1. Emicizumab is an effective bleeding prophylaxis in patient with AHA.
   Consensus: 100%.
2. Emicizumab should be considered for bleeding prophylaxis in patients with AHA from the time of diagnosis.
   Consensus: 100%.
3. Prior to the use of emicizumab in AHA, patients should be informed that emicizumab is currently not approved in patients with AHA.
   Consensus: 100%.

Dosing of Emicizumab

4. The loading dose is 6 mg/kg body weight on day 1 and 3 mg/kg body weight on day 2 if rapid bleeding prophylaxis is to be achieved.
   Consensus: 93.9%.
   Comment: This accelerated loading regimen was used in the AGEHA and the GTH-AHA-EMI trials but is not licensed. It achieved steady state levels of emicizumab within 1 week.
5. If there is a low bleeding tendency, saturation with 3 mg/kg body weight once a week for 4 weeks can be considered.
   Consensus: 78.8%.
   Comments: This is the approved loading regimen used in patients with congenital hemophilia A. It achieved steady state levels of emicizumab within 4 weeks of treatment. It was also used in case reports of emicizumab in AHA and in the Vienna series.[12,13]
6. The maintenance dose of emicizumab is 1.5 mg/kg body weight once per week.
   Consensus: 90.9%.
   Comments: This maintenance dose was used in the Japanese and the GTH-AHA-EMI studies. Case reports used lower or less frequent doses.

Control of Breakthrough Bleeding, Immunosuppression, and Follow-up

7. Breakthrough bleeds in patients with AHA on prophylaxis with emicizumab should be treated with rFVIIa or rpFVIII, but not with aPCC.
   Consensus: 97.0%.
   Comment: The use of aPCC was contraindicated in the GTH-AHA-EMI study because of its known interaction with emicizumab and the risk of thrombotic microangiopathy reported in trials of patients with congenital hemophilia A and inhibitors. In individual cases, bleeding was also managed with human FVIII.
8. Immunosuppression should be offered to patients on emicizumab if they are eligible based on physical status.
   Consensus: 97.0%.
   Comment: Immunosuppression was deferred for at least 12 weeks in the GTH-AHA-EMI study to evaluate the prophylactic efficacy of emicizumab without the confounding effect of remission. The Japanese study and several case reports used IST according to the discretion of the investigators.
9. Emicizumab should be discontinued when remission of AHA is achieved.
   Consensus: 97.0%.
   Comments: Earlier discontinuation can be considered in stable patients achieving FVIII >30%.
10. Under emicizumab therapy, the achievement of remission of AHA can only be monitored using the chromogenic FVIII assay with bovine substrate.
    Consensus: 100%.
11. Patients with AHA on prophylaxis with emicizumab should receive outpatient care in expert hemophilia care centers after hospital discharge.
    Consensus: 90.9%.
    Comments: If regular visits in the hemophilia care center are not possible, the local general physician or hematologist should collaborate closely with a hemophilia care center.

Statement Excluded Because No Consensus Was Reached

1. As an alternative to the maintenance dose of 1.5 mg/kg body weight once per week, 3 mg/kg body weight every 2 weeks, or 6 mg/kg body weight every 4 weeks can be applied.
   Consensus: 72.7%.
   Comments: These alternative regimens are derived from licensed regimens in congenital hemophilia A but have not been studied in AHA.

Discussion

This Delphi process was initiated by the members of the GTH-AHA study group to reach consensus on the use of emicizumab in the management of AHA in the context of the data generated from the GTH-AHA-EMI study. Based on the favorably low bleeding rates and promising survival observed in this study, all participants considered emicizumab as an effective bleeding prophylaxis that should be offered to AHA patients at the time of diagnosis. Patients should be informed about the off-label use as long as emicizumab is not licensed in AHA.

A consensus of 93.9% was achieved for the rapid saturation regimen with 6 mg/kg body weight on day 1 and 3 mg/kg body weight on day 2. This regimen was used in the GTH-AHA-EMI study and in the prospective AGEHA trial.[14] In both studies, mean emicizumab plasma levels were above 20 µg/mL at the end of week 1 and treatment with bypassing agents was stopped in most cases. Therefore, it should be the regimen of choice in AHA patients especially when rapid bleeding prophylaxis is needed. The saturation regimen consisting of 3 mg/kg body weight weekly for 4 weeks known from the HAVEN studies in patients with congenital hemophilia A[9–11] was discussed as an alternative option for patients with low bleeding tendency. This regimen was used in the case series of AHA patients published by Knoebl et al[13] and several case reports suggesting that lower doses could also be effective. This is in line with observations from patients with congenital hemophilia A showing that even low emicizumab plasma levels may result in an effective bleeding prophylaxis.[16,17] However, the AGEHA and GTH-AHA-EMI studies are currently the only prospectively studied dosing regimens in AHA.

The maintenance dose of emicizumab of 1.5 mg/kg body weight once weekly was considered the regimen of choice by 90.9% of the participants. The use of longer dosing intervals (e.g., 3 mg/kg every 2 weeks or 6 mg/kg every 4 weeks) was

discussed but did not reach consensus. The main concerns were raised about the long half-life of emicizumab, which may potentially result in overtreatment and higher cost in patients, who rapidly achieve remission. Longer time intervals may be suitable, however, in patients with chronic, IST-resistant AHA, patients not eligible for IST, and those who are expected to need long time to achieve remission.

Although emicizumab reduces the frequency of bleeding in AHA patients, it does not completely prevent the occurrence of breakthrough bleeding or even life-threatening bleeding. Strong consensus was found for the choice of rFVIIa and rpFVIII over aPCC for the treatment of breakthrough bleeding under emicizumab therapy, due to thrombotic microangiopathies that occurred during the HAVEN1 study in patients with congenital hemophilia A and inhibitors.[9] If rFVIIa and rpFVIII are not available, treatment with human FVIII concentrates may be used instead, especially in patients with low titer inhibitors.[1]

Apart from bleeding prophylaxis and treatment, immunosuppression for inhibitor eradication is a pillar of AHA treatment. A strong consensus was reached that immunosuppression should be offered to eligible patients based on their physical condition. Considering the high morbidity and mortality associated with immunosuppression and the fact that emicizumab is a very effective bleeding prophylaxis with few side effects, it is reasonable to offer immunosuppression only to patients who are deemed stable enough. This may include bleeding prophylaxis with emicizumab until patients have recovered from acute illness or infections. Nevertheless, some patients may not be eligible for immunosuppression due to preexisting comorbidities. Especially those patients will benefit from long-term bleeding prophylaxis with emicizumab. The ongoing AHAEmi trial (NCT05345197) will provide further data regarding the efficacy and safety of emicizumab in combination with immunosuppression.

All participants agreed that FVIII activity should only be measured using a chromogenic assay with bovine substrate to monitor remission in patients undergoing immunosuppression. A strong consensus was found that emicizumab should be discontinued when remission is achieved. Given the long half-life of emicizumab, the optimal timing for discontinuation of emicizumab needs further investigation. The treatment of AHA patients should be coordinated by specialized hemophilia centers. In more rural areas, a close collaboration of a local health care provider or hematologist with a hemophilia center was considered as an alternative.

Conclusion

This is the first consensus statement for the treatment of AHA with emicizumab. All participants had treated AHA patients with emicizumab during the GTH-AHA-EMI study and knew the results of the study prior to the initiation of the Delphi process. This knowledge led to a strong consensus that emicizumab is an effective bleeding prophylaxis and should be offered to AHA patients, although it is currently not approved. Inhibitor eradication with immunosuppression will still be required in most AHA patients. We are confident that most patients will benefit from early initiation of emicizumab prophylaxis to defer immunosuppression until patients have recovered from acute bleeding-related illness and to provide efficient bleeding prophylaxis until AHA is in remission.

Conflict of Interest

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