The changing landscape of treatment for acquired hemophilia A

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ABSTRACT

Acquired hemophilia A (AHA) is a rare acquired autoimmune disorder caused by autoantibodies against coagulation factor VIII (FVIII), which cause a hemorrhagic diathesis, not rarely of severe degree. Standard treatment consists of bleeding control with bypassing agents (recombinant activated factor VII and activated prothrombin complex concentrate) and recombinant porcine FVIII, and immunosuppressive therapy (corticosteroids with or without cyclophosphamide). Recent studies have renewed the interest towards the immunosuppressive agent rituximab for FVIII inhibitor eradication and have suggested a potential role for emicizumab for the prevention of bleeding in AHA patients. This narrative review will focus on the placement of these two emerging drugs within the treatment landscape for AHA.

Introduction

Acquired hemophilia A (AHA) is a rare autoimmune bleeding disorder caused by the development of autoantibodies against clotting factor VIII (FVIII). It is typically characterized by the sudden onset of bleeding diathesis in individuals without a family or personal history of hemorrhagic diseases.[1-4] Such clinical suspicion is confirmed by the laboratory evidence of prolonged activated partial thromboplastin time (aPTT), reduced clotting FVIII plasma levels, and laboratory detection of anti-FVIII autoantibodies. Although AHA is considered a rare bleeding disease (1.5 cases/million inhabitants/year, increasing with age), its incidence is certainly underestimated since physicians may have difficulty suspecting such a rare acquired disorder and therefore in making the proper diagnosis.[5] About half of the cases of AHA are idiopathic, while the other half are linked to an underlying condition, most commonly malignancies, autoimmune disorders (particularly rheumatoid arthritis, thyroid disorders and systemic lupus erythematosus), infections or vaccination (including SARS-CoV-2), drugs (particularly antibiotics and interferon), and pregnancy.[5-8]

The two pillars for the management of AHA consist of the treatment of bleeding first and then on the eradication of the inhibitor. The identification (when present) and treatment (when possible) of the underlying disorder is equally important, being associated with patients' outcome.[9-11] Effective first-line hemostatic options include bypassing agents (i.e., recombinant activated factor VII [rFVIIa] and activated prothrombin complex concentrate [aPCC]) as well as recombinant porcine factor VIII (rpFVIII, susoctocog alfa), while human FVIII concentrates are used as a secondary option due to a lower efficacy.[12-15] First-line eradication therapy for AHA includes steroids alone or in association with cyclophosphamide: the latter is indicated especially in patients with poor-prognosis (i.e. those with FVIII <1%, and inhibitor titer >20 Bethesda units [BU] at diagnosis).[16] Immunosuppressive therapy (IST), in particular the combination of steroids and cyclophosphamide, is burdened by an increased risk of serious infections, which often exceeds the risk of fatal bleeding.[12,16-18]

While there is a renewing interest towards the immunosuppressive agent rituximab, recent studies suggest the potential clinical efficacy of the hemostatic agent emicizumab in preventing bleeding events also in AHA patients. This narrative review provides an update on the clinical use of these two latter agents in AHA, focusing on the results from the latest trials. Finally, this paper will not focus on susoctocog alfa because this hemostatic agent, although recently introduced, is considered an effective and well established first-line therapeutic option in AHA.[15]

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Key words: acquired hemophilia; FVIII inhibitor; rituximab; emicizumab.

Contributions: all the authors contributed equally, read and approved the final version of the manuscript and agreed to be accountable for all aspects of the work.

Conflict of interest: the authors declare no potential conflict of interest.

Ethical approval: not applicable.

Received: 8 October 2024.
Accepted: 20 January 2025.

Bleeding, Thrombosis and Vascular Biology 2025; 1:157
doi:10.4081/btvb.2025.157

Rituximab

Rituximab is an anti-CD20 monoclonal antibody currently approved for the treatment of non-Hodgkin's lymphoma, B-cell chronic lymphocytic leukemia, rheumatoid arthritis, granulomatosis with polyangiitis, microscopic polyangiitis, and pemphigus vulgaris. In addition, rituximab has been increasingly utilized off-label in a variety of autoimmune disorders worldwide.[19] In this regard, several reports have been published over the last twenty years about the clinical benefit of rituximab in AHA patients.[20-22] The results from the prospective EACH2 Registry, published in 2012, showed that patients treated with a rituximab-based regimen achieved a lower (59% *vs* 70%) and later (65 days *vs* 32 days), although longer lasting, complete response rate than that achieved by AHA patients treated with other immunosuppressive agents (i.e., steroids and cyclophosphamide).[23] In a retrospective analysis from China including 165 AHA cases, 93% of patients treated with rituximab-based therapy achieved a complete remission, percentage higher than that achieved in patients receiving steroids and cyclophosphamide (85%) or steroids alone (82%).[24] Although in most trials rituximab was administered at the classical intravenous (IV) dosage of 375 mg/m^2 once weekly for four weeks in association with steroids, a recent retrospective study from Hungary investigated in 32 AHA patients a different protocol (named CyDRi) including a lower dosage of rituximab (100 mg IV on days 1, 8, 15 and 22) associated with cyclophosphamide (1000 mg IV on days 1 and 22) and dexamethasone (40 mg IV or by mouth on days 1, 8, 15 and 22). The results from such triple pulsed treatment regimen, designed to reduce the toxic adverse effects (in particular infections) of IST, were very encouraging, with 97% of patients achieving a durable remission and a low rate of side effects.[25]

Considering the results available from the literature, mostly coming from case series, data from registries or retrospective studies, the recommendations from international guidelines on AHA were cautious regarding rituximab, supporting it as second-line therapy after failure of first-line immunosuppressive agents (i.e., steroids and cyclophosphamide), or as first-line therapy in patients with contraindication to steroids or cyclophosphamide,[5] or in the presence of poor prognostic markers (i.e., those with FVIII <1% or inhibitor titer >20 BU).[10] Our evidence base on the clinical effectiveness and safety of rituximab in AHA has greatly improved in the last year thanks to the publication of two randomized controlled trials (RCTs). In the first noninferiority, open-label, multicenter RCT, 63 Chinese patients with newly diagnosed AHA were randomly assigned to receive methylprednisolone (0.8 mg/kg per day for the first 3 weeks and then tapered) plus single-dose rituximab (375 mg/m^2) or plus cyclophosphamide (2 mg/kg per day until inhibitor disappearance, for a maximum of 5 weeks). Twenty-four of the 31 (77%) patients in the rituximab group and 22 of the 32 (69%) patients in the cyclophosphamide group achieved complete remission, which showed the noninferiority of the single-dose rituximab-based regimen (absolute difference=-8.67%, p for noninferiority = 0.005). No difference was found in the incidence of treatment-related adverse events. Considering that these reassuring results show a similar efficacy of a rituximab-based regimen versus a cyclophosphamide-based regimen, the authors recommended single-dose rituximab plus glucocorticoids as a first-line therapy for AHA, due to lower long-term toxicity (i.e., secondary malignances and reproductive toxicity) than cyclophosphamide, especially in young patients (the majority of patients enrolled in the RCT were below 50 years of age).[26] Another open-label, RCT from France randomized 108 AHA patients to receive steroids (1 mg/kg/day orally for 6 weeks or until remission) plus either cyclophosphamide (1.5-2 mg/kg/day orally for 6 weeks or until remission) or rituximab (375 mg/m^2 IV once weekly for four weeks). After 18 months of follow-up a similar rate of complete remissions was observed in the two arms (67% versus 62%; OR 1.26; 95% CI 0.57-2.78), with also comparable safety data, in particular regarding the risk of infections.[27] Notably, in the poor prognosis group (FVIII <1% or inhibitor titer > 20 BU) significantly more remissions were observed in patients treated with steroids plus cyclophosphamide than in those treated with steroids plus rituximab (79% *vs* 48%, p=0.02). Differing from the previous RCT, the authors concluded in favor of the association prednisone plus cyclophosphamide due to the lower costs and the easier route of administration.[27]

All in all, the evidence from the literature, improved by the recent acquisition from those two RCTs, supports the long-term efficacy and safety of rituximab at eradicating AHA autoantibodies. This agent, therefore, could be considered as a first-line therapeutic option in selected categories of AHA patients, such as those of younger age.

Emicizumab

The bispecific monoclonal antibody emicizumab, by mimicking the function of activated FVIII (FVIIIa) in the coagulation cascade, has revolutionized the management of congenital hemophilia A, being currently licensed for bleeding prophylaxis in patients with or without FVIII inhibitors.[28] Due to its undoubted advantages over traditional replacement therapy (i.e., the subcutaneous route of administration and the long half-life of 28 days), emicizumab has been investigated in other bleeding conditions characterized by FVIII deficiency, including severe von Willebrand disease and AHA.[29-31] Regarding the latter disease, in most reports emicizumab was used as prophylaxis of recurrence after the control of bleeding with bypassing agents, while in some studies it was a second-line treatment of acute bleeding after failure of first-line approaches.[32]

Knoebl and colleagues reported on 12 high-risk AHA patients treated with emicizumab, which was started at 3 mg/kg subcutaneously weekly for 2 to 3 doses, followed by a maintenance with 1.5 mg/kg every 3 weeks.[33] A rapid improvement in bleeding symptoms was observed (bypassing therapy was stopped after a median of 1.5 days) with no safety concerns (no patient died of bleeding or thromboembolism). On the basis of these results, the authors concluded that emicizumab seems to be an effective hemostatic therapy for AHA, with the advantages of subcutaneous therapy, good hemostatic efficacy, early discharge, and reduction of immunosuppression and adverse events.[33] Growing evidence of the clinical benefit of this FVIIIa mimetic therapy has come, however, from more recent trials.[34] A prospective, multicenter, open-label phase III study (AGEHA) conducted in Japan investigated the efficacy, safety, pharmacokinetics and pharmacodynamics of prophylaxis with emicizumab in 12 patients with AHA.[35,36] Interestingly, the use by the investigators of a more aggressive dosing regimen (loading dose of 6 mg/kg on day 1, 3 mg/kg on day 2, followed by a maintenance dose of 1.5 mg/kg once weekly

from day 8 thereafter) than that usually adopted for congenital hemophilia A (i.e., loading dose of 3 mg/kg/week for 4 weeks followed by a maintenance dose of 1.5 mg/kg/week, 3 mg/kg every 2 weeks or 6 mg/kg every 4 weeks from the fifth week onwards) led to an earlier clinical response (1 week versus 4 weeks with standard emicizumab dosing regimen) which consequently reduced the requirement for bypassing therapy and the annualized bleeding rate (ABR) from 66.4 to zero for all major bleeds.[35,36] In addition, tailored IST approaches (delayed, reduced, or no therapy) were successfully performed thanks to emicizumab prophylaxis.[36] Considering the clinical relevance of IST-related infections, an open-label German phase 2 clinical trial (GTH-AHA-EMI) investigated in 47 AHA patients the early and rapid initiation of emicizumab (loading dose of 6 and 3 mg/kg on days 1 and 2, maintenance dose of 1.5 mg/kg weekly from day 8 onwards until week 12) and the deferral of IST by 12 weeks.[37] This study showed that this high-dose emicizumab prophylaxis regimen, aimed at achieving an earlier and more rapid hemostasis, was safe and effective in preventing most bleeding (70% of patients had no bleeding events), permitting the delay of immunosuppression for 12 weeks, thus avoiding infections and other adverse complications typically seen in this cohort of patients with AHA. Finally, a propensity-score matching analysis comparing the outcomes from the prospective trials that used either IST (GTH-AH 01/2010) or emicizumab prophylaxis (GHT-AHA-EMI) early after AHA diagnosis suggested that patients on emicizumab experienced better bleed protection, improved overall survival and reduced fatal infections compared with patients treated with immediate IST.[38] Although this newer evidence from the literature suggests a prominent role of emicizumab in the therapeutic landscape of AHA,[34] particular attention must be paid to the safety profile of emicizumab. In the context of the post-marketing surveillance of emicizumab conducted by the license holder, among a total of 56 thrombotic complications in more than 11,400 cases treated in 100 different countries, 7 occurred in patients with AHA receiving off-label emicizumab.[39] A recent systematic review of the literature documented 3 emicizumab-related thromboembolic events among 73 AHA cases and a warning was given by the authors about the use of this monoclonal antibody in AHA patients with additional prothrombotic factors, such as older people, cancer patients, and women during childbirth or postpartum.[30] In addition, translating the evidence from patients with congenital hemophilia with inhibitors, we recommend particular caution in using aPCC in patients with breakthrough bleeding while on emicizumab prophylaxis.[28]

Conclusions

Acquired hemophilia A is an autoimmune disorder characterized by sudden and potentially life-threatening hemorrhagic episodes. The dual goal of the therapy is that of managing bleeds and eradicating the anti-FVIII autoantibody. The efforts of the investigators in this field have been focused in the last years on the development of therapeutic protocols aimed at improving the treatment and prevention of bleeding events and at reducing the toxic effects of immunosuppressive agents, considering that immunosuppression-related infections are among the main causes of death in AHA patients, especially in those elderly and frail.

In this context, there has been an increasing interest towards the anti-CD20 monoclonal antibody rituximab, thanks to the results from two recent RCTs showing its efficacy and safety in eradicating FVIII autoantibodies. Despite this evidence, however, rituximab is still an off-label, unlicensed treatment in AHA, and we then recommend an urgent revision of its treatment indications.

The same argument applies to emicizumab which, as is happening for congenital hemophilia, is also revolutionizing the management strategy of patients affected by AHA, providing a fast and effective hemostatic control and delaying the potentially toxic IST. A number of issues regarding the AHA treatment with emicizumab are, however, still opened, including the optimal dosing (i.e., loading versus standard dose), its impact on timing and dosing of IST, the potential thrombotic risk (in particular, during the IST-induced FVIII levels increase while on emicizumab) and the management of breakthrough bleeds.[34,40,41] For this reason, we recommend a patient by patient careful evaluation of the risks and benefits before using emicizumab in this clinical setting.

Finally, the newer therapeutic protocols for AHA including emicizumab and rituximab need to be verified in real-life clinical practice trials evaluating the long-term safety and effectiveness of these agents in larger number of patients, and their economical sustainability.

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