Literature review

Anti-factor VIII autoantibody eradication in acquired hemophilia A: focused strategies for resource-constrained settings

Chatphatai Moonla[1,2,3], Patrick Ellsworth[3,4] and Nigel S. Key[3,4]

[1]Division of General Internal Medicine, Department of Medicine, Faculty of Medicine, Chulalongkorn University and King Chulalongkorn Memorial Hospital; [2]Center of Excellence in Translational Hematology, Faculty of Medicine, Chulalongkorn University; [3]UNC Blood Research Center, Department of Medicine, University of North Carolina at Chapel Hill, Chapel Hill, NC, USA.; [4]Division of Hematology, Department of Medicine, University of North Carolina at Chapel Hill, Chapel Hill, NC, USA.

Introduction

Acquired hemophilia A (AHA) is an uncommon, but serious, hemostatic disorder characterized by a deficiency of coagulation factor VIII (FVIII) due to the development of autoantibodies against FVIII, with an incidence of 1-1.5 cases per 1 million persons per year.[1] Unlike congenital hemophilia A (CHA), where anti-FVIII alloantibodies develop following exposure to exogenous FVIII, anti-FVIII autoantibodies spontaneously arise to neutralize endogenous FVIII in AHA. Although approximately 44-52% of patients with AHA are idiopathic, several cases are associated with hematologic or non-hematologic malignancies (6-18%) and autoimmune diseases (9-17%), e.g., rheumatoid arthritis and systemic lupus erythematosus.[2] In general, AHA predominantly affects the elderly, with a median age at diagnosis between 64 and 78 years, but it can occur in younger patients, including those during the peripartum period.[2,3] Clinically, bleeding into subcutaneous tissues and skeletal muscles is the most reported manifestation (> 80%), while joint bleeding, which is common in CHA, rarely occurs in AHA.[1-3]

Basic coagulation tests showing an isolated prolongation of activated partial thromboplastin time (aPTT), uncorrectable with a mixing study, and a low FVIII coagulant activity (FVIII:C) level would preliminarily lead to the diagnosis of AHA; however, anti-FVIII autoantibodies need to be confirmed by the Nijmegen-modified Bethesda assay.[2,3] Anti-FVIII autoantibodies at lower concentrations can neutralize FVIII more effectively than those at higher concentrations during the phase of equilibrium, representing their unique second-order kinetics. Anti-FVIII autoantibody titers, therefore, do not predict residual FVIII:C levels in AHA.[1] Conversely, in CHA, the ability to neutralize FVIII is proportional to anti-FVIII alloantibody levels, reflecting their first-order kinetics. Consequently, FVIII:C detectable ex vivo regardless of anti-FVIII autoantibody levels may not correlate with the actual risk of bleeding in AHA, although FVIII:C of < 1 IU/dL is occasionally observed in a small number of patients, and has been associated with a poorer prognosis.[1,3]

Hemostatic therapy with bypassing agents (BAs), i.e., recombinant activated factor VII (rFVIIa) and activated prothrombin complex concentrate, and recombinant porcine FVIII concentrate are efficacious in rescuing breakthrough bleeding.[4-8] Additionally, emicizumab, a novel FVIII-mimetic bispecific monoclonal antibody (mAb) which is indicated for prophylactic therapy in patients with CHA with/without anti-FVIII alloantibodies, has been reported to effectively protect against rebleeding in AHA.[9] However, these agents are significantly costly and may not be readily available in resource-limited settings, potentially causing financial

Correspondence should be addressed to Chatphatai Moonla, MD, MSc, Department of Medicine, Faculty of Medicine, Division of Hematology, Department of Medicine, Faculty of Medicine, Chulalongkorn University and King Chulalongkorn Memorial Hospital, Rama 4 Rd., Pathumwan, Bangkok 10330 E-mail: chatphatai.moonla@gmail.com, chatphatai.m@chula.ac.th Tel: +66-2256-4000 EXT 61834; Fax: +66-2256-4000 EXT 80255

burdens. Furthermore, despite the fact that low-titer anti-FVIII autoantibodies (≥ 0.6 but < 5.0 Bethesda units [BU]/mL) might spontaneously resolve within several months after diagnosis, patients with symptomatic bleeding, especially those with high-titer anti-FVIII autoantibodies (≥ 5.0 BU/mL), continue to be at risk of rebleeding and increased bleeding-related mortality.[1-3] Eradicating anti-FVIII autoantibodies with an appropriate immunosuppressive therapy (IST), therefore, remains a standard intervention for most patients with AHA.[2,3] Not only does it definitively cure the disease but also fully restores endogenous FVIII levels, ultimately leading to the termination of hemostatic treatments.

This review aims to summarize current evidence on anti-FVIII autoantibody eradication strategies for AHA, considering the limitations of AHA management in countries with significant resource and budget constraints. Perspectives on opportunities to implement novel therapies for AHA are also discussed in this focused context.

First-line immunosuppressive therapy

Traditionally, corticosteroid monotherapy or combined IST regimens using corticosteroids plus other immunosuppressants, including cyclophosphamide and/or rituximab, are commonly used as first-line IST for AHA.[1-3] Over the past 3 decades, several clinical studies have accumulated data on patients with AHA around the world, reporting the use of various IST regimens and providing insights into their efficacy, times to remission, and relapse rates in AHA.[10-19]

Corticosteroid monotherapy

Corticosteroid monotherapy has been a classical first-line IST, due to its affordability and well-known safety on a short-term course in the majority of patients, even those with pregnancy-associated AHA.[1-3] Nonetheless, according to 2 landmark cohort studies conducted in the 2000s, i.e., the United Kingdom Haemophilia Centre Doctors' Organisation (UKHCDO) surveillance study and the European Acquired Haemophilia Registry (EACH2), the complete remission (CR) rates and times to CR induced by corticosteroid monotherapy varied significantly.[10,11] In the UKHCDO surveillance study (n = 172), corticosteroid monotherapy (oral prednisolone 1 mg/kg/day), which was prescribed in 26% of patients, led to CR (FVIII:C normalization and undetectable anti-FVIII autoantibodies with IST stopped or reduced to pre-AHA doses without relapse) in 76% of patients, with a median time to CR of 7.0 weeks.[10] Meanwhile, in the EACH2 (n = 331), corticosteroid monotherapy (oral prednisolone 1 mg/kg/day or equivalent intravenous dexamethasone) was used in 43% of patients; however, the CR rate was lower at 58% with a longer median time to CR of 15.4 weeks and a relapse rate of 18% at a median time of 19.1 weeks after achieving CR.[11]

Subsequent cohort studies also showed heterogeneity of remission rates and median times to remission after corticosteroid monotherapy.[12-18] The Dutch cohort study (n = 143) reported the use of corticosteroids alone (oral prednisolone 1 mg/kg/day) in 68% of patients diagnosed with AHA from 1992 to 2018 in the Netherlands, resulting in the CR rate of only 35% with a median time to CR of 6.9 weeks and a relapse rate of 26%.[12] In contrast, the AHA Spanish Registry (n = 147), which collected patients with AHA between 2014 and 2020 in Spain, revealed a lower rate of corticosteroid monotherapy in only 15% of patients. Despite that, 68% of patients in this group achieved CR in a median time of only 4.3 weeks.[13] In Germany, Austria, and Switzerland, the GTH-AH 01/2010 study (n = 102), which started using the sequential IST protocol in 2010 and uniquely determined partial response (PR; FVIII:C restoration to > 50 IU/dL without any bleeding after hemostatic agents were discontinued for 24 hours), demonstrated that 47% of patients with AHA who received corticosteroids alone (oral prednisolone 1-1.5 mg/kg/day) could achieve PR in a median time of 4.1 weeks.[14]

In Asia, where resource limitations are generally greater and AHA tends to affect younger populations (mean age at diagnosis of 52-58 years),[15-17] the China

Acquired Hemophilia Registry (CARE; n = 187) showed that corticosteroid monotherapy (oral prednisolone 1 mg/kg/day or equivalent intravenous dexamethasone) was used in only 20% of patients with AHA from 2012 to 2017. The PR and CR rates were 70% and 62%, respectively, with a median time to CR of 9.8 weeks and a relapse rate of 22%.[15] In Thailand, the proportions of patients with AHA treated with corticosteroids alone (oral prednisolone 0.5-1 mg/kg/day with/without initial pulse intravenous/oral dexamethasone 20-40 mg/day for 4 days) ranged from 8% to 84% among 3 studies (n = 116), with 50-74% of patients achieving CR at median times ranging from 7.1 to 9.0 weeks.[16-18]

Overall, corticosteroid monotherapy may induce PR and CR in approximately 47-70% and 35-76% of patients with AHA, and requires several weeks to months to respond. Furthermore, it should be noted that most studies analyzed their data irrespectively of the risk factors of prognostication, and there were significant differences in the IST protocols between studies based on local policies and evolving recommendations over time. Therefore, although corticosteroids alone can be considered as an appropriate choice of first-line IST for most patients with AHA, some patients require an escalation of IST for anti-FVIII autoantibody eradication.

Combined immunosuppressive therapy

Several immunosuppressants have been combined with corticosteroids to treat AHA. While those reported in the literature include cytotoxic agents (e.g., cyclophosphamide, calcineurin inhibitors, azathioprine) and the anti-CD20 mAb rituximab; cyclophosphamide and rituximab are most commonly used.[10-19] Combined IST can be implemented from the initiation of treatment or as a rescue regimen after an inadequate response to corticosteroid monotherapy.[2,3]

1. Cyclophosphamide combination

The addition of oral cyclophosphamide (1-2 mg/kg/day) to corticosteroids was applied in 12-84% of patients with AHA in previous cohort studies.[10-13,15,18] The CR rates ranged between 75-89%, with median times to CR of 7.6-10.6 weeks and relapse rates of 5-12% after IST was stopped. In the GTH-AH 01/2010 study, where cyclophosphamide was added only to patients with AHA who failed to respond to corticosteroid monotherapy within 4 weeks, the corticosteroid-cyclophosphamide combination eventually induced PR in 60% of these patients.[14]

Compared with corticosteroids alone, the significantly higher PR or CR rates achieved by corticostroid-cyclophosphamide regimens were shown in most studies, while times to response in the corticosteroid-cyclophosphamide group were variable.[11-13,15,18] Nevertheless, a recent meta-analysis (47 studies; n = 2112) demonstrated that the corticosteroid-cyclophosphamide combination could induce higher CR and relapse-free rates than corticosteroids alone. In the corticosteroid-cyclophosphamide group, the weighted mean CR rate, time to CR, and relapse rate were 76%, 8.2 weeks, and 14%, respectively, compared with 67%, 8.8 weeks, and 24%, in the corticosteroid monotherapy group.[18] Despite the modestly improved outcomes, the corticosteroid-cyclophosphamide combination might adversely result in greater regimen-related toxicity, such as infections (9-38% vs. 7-16% with corticosteroids alone) and neutropenia (14-25% vs. 0-1% with corticosteroids alone).[10-12]

2. Rituximab-based regimens

Rituximab, an anti-CD20 mAb targeting mature B-cells, has been widely used as a therapeutic option for immune-mediated diseases, including AHA.[20] The proportions of patients with AHA who were treated with rituximab-combining IST regimens increased from < 1% in the UKHCDO surveillance study to 15% in the EACH2 during the 2000s, and further increased to 22-28% in subsequent cohort studies during the 2010s.[10-13,15] Dosages of intravenous rituximab used in IST regimens varied between studies, commonly reported as 375 mg/m^2 once a week for 4 weeks, 100 mg once a week for 4 weeks, and 1,000 mg every other week for 2 doses. Rituximab could be combined with either corticosteroids alone, corticosteroids plus cyclophosphamide, or

other cytotoxic agents; rituximab monotherapy was also applied in a few case series. Although the efficacy of the corticosteroid-rituximab combination was exhibited in some studies,[11,12] most studies cumulatively analyzed data of rituximab-based regimens without a subgroup analysis.

Based on large cohort studies, the CR rates and median times to CR in patients with AHA who received rituximab-based regimens ranged from 61% to 91%, and from 6.0 to 9.3 weeks, respectively.[11-13,15,18,19] The meta-analysis also confirmed that rituximab-based regimens yielded higher CR and relapse-free rates than corticosteroid monotherapy. The pooled relapse rate was only 6% in the rituximab group, although the weighted mean time to CR was not shortened, and no significant differences in the CR and relapse rates were observed between the groups of rituximab-based and corticosteroid-cyclophosphamide regimens.[18] Furthermore, when rituximab was used to rescue patients who had been treated with corticosteroids with/without cyclophosphamide for 6 weeks without achieving PR, the corticosteroid-rituximab combination yielded an improved response with a PR rate of 71%.[14] Despite the promising efficacy, those receiving rituximab-based regimens experienced higher rates of infection (12-40%) and neutropenia (18-40%) compared to those treated with corticosteroids alone.[11,12]

Corticosteroid-cyclophosphamide and corticosteroid-rituximab regimens were directly compared in 2 recent randomized trials.[21,22] In the French study (CREHA; n = 108), patients newly diagnosed with AHA during 2012-2019 were treated with corticosteroids (oral prednisone 1 mg/kg/day) and randomly assigned to receive either oral cyclophosphamide 1.5-2 mg/kg/day for 6 weeks (n = 58), or intravenous rituximab 375 mg/m^2 once a week for 4 weeks (n = 50).[21] Within 18 months of follow-up, the CR rates in the corticosteroid-cyclophosphamide and corticosteroid-rituximab groups were not significantly different (67% vs. 62%). In the corticosteroid-cyclophosphamide group, a median time to CR, relapse and infection rates were 6.6 weeks, 11% and 33%, respectively, similar to 6.9 weeks, 7% and 40%, in the corticosteroid-rituximab group. Concurrently, in the Chinese study conducted during 2017-2022 (n = 63), patients with newly diagnosed AHA were treated with oral methylprednisolone 0.8 mg/kg/day for 3 weeks followed by tapered withdrawal over 5 weeks, in combination with either oral cyclophosphamide 2 mg/kg/day for a maximum of 5 weeks (n = 31) or intravenous rituximab 375 mg/m^2 only once (n = 32).[22] As soon as anti-FVIII autoantibodies became negative, cyclophosphamide was abruptly discontinued. Based on a non-inferiority margin of 20% difference in the CR rate within 8 weeks, the efficacy of the corticosteroid-cyclophosphamide combination was not inferior to corticosteroids plus single-dose rituximab (69% vs. 77%). Median times to CR and relapse rates were not significantly different between the groups. Infections tended to occur in the rituximab-treated group (19%) higher than the cyclophosphamide-treated group (9%), but did not reach statistical significance.

Recently, the Hungarian study group introduced a novel IST regimen (termed the "CyDRi protocol") containing intravenous cyclophosphamide (1,000 mg on days 1 and 22), intravenous/oral dexamethasone (40 mg once a week for 4 weeks), and intravenous rituximab (100 mg once a week for 4 weeks) to treat patients with AHA (n = 32).[23] A repeat CyDRi cycle was allowed every 6 weeks if CR was not reached. After 1-9 CyDRi cycles, CR was attained in 97% of patients; 69% of whom received only 1 cycle. Although the median time to CR was 11.0 weeks, longer than those reported for other combined IST regimens, only 7% and 15% of CyDRi-treated patients experienced a relapse and infectious complications, respectively. The low incidence of infections after the CyDRi regimen may be attributable to the relatively low exposure to corticosteroids, compared to previously investigated IST protocols.[10-12,21,22] Due to its excellent performance with acceptably low toxicity, the CyDRi regimen may be a valuable IST option for AHA when higher doses of rituximab are less accessible.

Table 1 Key efficacy outcomes of first-line immunosuppressive therapy for anti-factor VIII autoantibody eradication in risk factor-unstratified patients with acquired hemophilia A based on the selected landmark studies.

Study	First-line IST regimen	CR rate	Median time to CR	Relapse rate
UKHCDO surveillance study[10]	Corticosteroids alone	76.5%	7.0 weeks (95%CI: 4.4-8.9)	20.0% (whole cohort)
	Corticosteroid-cyclophosphamide combination	77.8%	5.6 weeks (95%CI: 4.9-8.1)	
EACH2[11]	Corticosteroids alone	58.5%	15.4 weeks (IQR, 7.9-29.7)	18.1%
	Corticosteroid-cyclophosphamide combination	79.5%	10.5 weeks (IQR, 7.4-21.6)	12.1%
	Rituximab-based regimens	60.8%	6.1 weeks (IQR, 3.1-13.7)	3.2%
Dutch cohort study[12]	Corticosteroids alone	35.2%	6.9 weeks (IQR, 5.0-11.7)	25.8%
	Corticosteroid-cyclophosphamide combination	80.0%	10.7 weeks (IQR, 5.6-27.1)	10.0%
	Rituximab-based regimens	66.7%	6.3 weeks (IQR, 3.9-11.8)	25.0%
AHA Spanish Registry[13]	Corticosteroids alone	68.2%	4.3 weeks (IQR, 2.1-3.1)	7.1% (whole cohort)
	Corticosteroid-cyclophosphamide combination	88.5%	7.6 weeks (IQR, 4.4-11.7)	
	Rituximab-based regimens	87.5%	6.0 weeks (IQR, 3.7-12.0)	
GTH-AH 01/2010 study[14]	Sequential IST (escalated if PR not achieved) Corticosteroids alone (weeks 1-3) Cyclophosphamide (weeks 4-6) Rituximab (weeks 7-10)	60.8%	11.3 weeks (IQR, 6.9-14.6)	24.2% (whole cohort)
CARE[15]	Corticosteroids alone	62.2%	9.9 weeks (IQR, 6.9-16.7)	21.7%
	Corticosteroid-cyclophosphamide combination	87.5%	8.9 weeks (IQR, 5.0-14.0)	5.4%
	Rituximab-based regimens	90.9%	6.7 weeks (IQR, 3.9-13.0)	5.0%
CREHA study[21]	Corticosteroid-cyclophosphamide combination	67.2%	6.6 weeks (IQR, 6.1-8.4)	11.1%
	Corticosteroid-rituximab combination	62.0%	6.9 weeks (IQR, 6.4-7.2)	7.3%
Chinese non-inferiority trial[22]	Corticosteroid-cyclophosphamide combination	68.8%	5.1 weeks (IQR, 3.4-7.2)	6.3%
	Corticosteroid-rituximab combination	77.4%	4.0 weeks (IQR, 3.0-7.5)	6.5%
CyDRi regimen[23]	Combined IST*	96.9%	11.0 weeks (IQR, 4.4-16.4)	6.5%

AHA, acquired hemophilia A; CARE, China Acquired Hemophilia Registry; CI, confidence interval; CR, complete remission; CREHA, Cyclophosphamide versus Rituximab Et Hémophilie Acquise; EACH2, European Acquired Haemophilia Registry; GTH-AH, Acquired Hemophilia Working Group of the German, Austrian, and Swiss Thrombosis and Hemostasis Society; IQR, interquartile range; IST, immunosuppressive therapy; PR, partial response; UKHCDO, United Kingdom Haemophilia Centre Doctors' Organisation.

*Corticosteroids (intravenous/oral dexamethasone 40 mg weekly for 4 weeks) plus cyclophosphamide (intravenous 1,000 mg on days 1 and 22) and rituximab (100 mg weekly for 4 weeks), repeatable every 6 weeks if CR was not reached.

In summary, compared with corticosteroid monotherapy, first-line corticosteroids combined with cyclophosphamide and/or rituximab may provide a higher likelihood of remission and lower relapse rates in risk factor-unstratified AHA populations (Table 1). Combined IST regimens can also help induce a response in patients who did not respond adequately to corticosteroids alone. However, due to the possible increase in toxicity associated with combined IST, the choice of IST regimen should be carefully tailored, considering the disease severity, patient co-morbidities, potential adverse effects, and available therapeutic options. A risk prediction model to forecast unresponsiveness to corticosteroid monotherapy would help clinical decision-making in the choice of first-line IST for patients with AHA.

Risk factor-stratified immunosuppressive therapy

From the GTH-AH 01/2010 study, factors associated with a poorer response to corticosteroids alone were identified.[14] Patients with FVIII:C < 1 IU/dL achieved PR (77%; median time to PR of 6.1 weeks) less often than those with FVIII:C ≥ 1 IU/dL (89%; median time to PR of 3.4 weeks). The CR and overall survival rates were also lower in patients with FVIII:C < 1 IU/dL. Furthermore, patients with anti-FVIII autoantibody titers ≥ 20 BU/mL were less likely to achieve PR within 21 days, compared to those with anti-FVIII autoantibody titers < 20 BU/mL. The impact of anti-FVIII autoantibody titers ≥ 20 BU/mL on failure to respond to any IST regimen was re-validated in the Dutch cohort study and the CREHA study.[12,21] These authors suggested that FVIII:C < 1 IU/dL and anti-FVIII autoantibody titers ≥ 20 BU/mL at presentation could indicate a poor prognosis for patients with AHA.[3] Since combined IST protocols potentially perform better in eradicating anti-FVIII autoantibodies, corticosteroid-cyclophosphamide or rituximab-based regimens rather than corticosteroids alone may be suitable as first-line IST for patients with poor prognostic factors, leading to the concept of a risk factor-stratified IST approach.

The risk factor-stratified IST strategy, which was modified from the sequential IST regimen of the GTH-AH 01/2010 Study, was evaluated in a single-center study in Germany.[24] Good-risk patients with AHA (FVIII:C ≥ 1 IU/dL and anti-FVIII autoantibody titers < 20 BU/mL) started with oral dexamethasone 40 mg/day on 4 consecutive days in weeks 1, 2, 5, and 6. Intravenous rituximab 375 mg/m^2 given once a week for 4 weeks was added in weeks 3-6, and intravenous cyclophosphamide 750 mg/m^2 was given every fortnight, started in week 8, for a maximum of 2 doses. In poor-risk patients with AHA (FVIII:C < 1 IU/dL or anti-FVIII autoantibody titers ≥ 20 BU/mL), the same dosages of dexamethasone were used, but rituximab (weeks 1-4) and cyclophosphamide (weeks 5) were scheduled to be administered earlier. As soon as PR was achieved, IST was discontinued without tapered withdrawal of corticosteroids. The study showed that 42% of good-risk patients received corticosteroids alone while 69% of poor-risk patients received the corticosteroid-rituximab combination without escalation to cyclophosphamide. Despite a median time to PR of 16.0 weeks, longer than that observed in the GTH-AH 01/2010 study, the overall PR rate was 68% without significant differences in any outcomes between good-risk and poor-risk patients. These data thus appear to support the hypothesis that poor-risk patients with AHA should be initially treated with a combined IST regimen rather than corticosteroids alone.

Since 2020, the updated international recommendations on the diagnosis and treatment of AHA by Tiede et al. have endorsed the risk factor-stratified IST approach by proposing the modified sequential IST regimens based on the presence/absence of poor prognostic factors.[3] These regimens were adapted from previously investigated IST protocols, including that used in the GTH-AH 01/2010 study. In good-risk patients with AHA, first-line corticosteroids alone were recommended. However, if no adequate response was seen, defined as PR or CR achieved within 3-4 weeks, cyclophosphamide or rituximab should be added. In poor-risk patients, the

Table 2 Risk factor-stratified immunosuppressive therapy proposed by the 2020 international recommendations on the diagnosis and treatment of acquired hemophilia A.[3]

IST regimen	Recommended dosage
Good-risk patients with AHA (FVIII:C ≥ 1 IU/dL and anti-FVIII autoantibody titers < 20 BU/mL)	
First-line corticosteroids alone	Oral prednisolone 1 mg/kg/day for a maximum of 4-6 weeks, followed by tapered withdrawal
Addition of second-line cyclophosphamide or rituximab (if PR not achieved within 3-4 weeks of first-line corticosteroid monotherapy)	Oral cyclophosphamide 1.5-2 mg/kg/day for a maximum of 6 weeks or intravenous rituximab 375 mg/m^2 weekly for a maximum of 4 doses
Poor-risk patients with AHA (FVIII:C < 1 IU/dL or anti-FVIII autoantibody titers ≥ 20 BU/mL)	
First-line corticosteroids plus cyclophosphamide or rituximab	Oral prednisolone 1 mg/kg/day for a maximum of 4-6 weeks, followed by tapered withdrawal, plus oral cyclophosphamide 1.5-2 mg/kg/day for a maximum of 6 weeks or intravenous rituximab 375 mg/m^2 weekly for a maximum of 4 doses
Addition of second-line cyclophosphamide or rituximab whichever was not used during first-line IST (if PR not achieved within 3-4 weeks of first-line combined IST)	Oral cyclophosphamide 1.5-2 mg/kg/day for a maximum of 6 weeks or intravenous rituximab 375 mg/m^2 weekly for a maximum of 4 doses, whichever was not used during first-line combined IST

AHA, acquired hemophilia A; BU, Bethesda unit; FVIII, factor VIII; FVIII:C, factor VIII activity; IST, immunosuppressive therapy; PR, partial response.

corticosteroid-cyclophosphamide or corticosteroid-rituximab combination was recommended as first-line IST. If PR was not achieved within 3-4 weeks, cyclophosphamide or rituximab (whichever was not used during the first combination regimen) should be added. Although the efficacy of this modified IST approach remains to be confirmed in future studies, the recommendations can assist clinicians to manage AHA more precisely. This IST approach is also feasible in resource-limited countries. The details of these sequential IST regimens stratified by prognostication risk factors are described in Table 2.

Regimens containing other targeted immunosuppressants

In addition to rituximab, an anti-CD20 mAb, several immunosuppressants targeting surface antigens or intracellular molecules of the immune cells involved in the pathogenesis of autoimmunity have been used in combination with corticosteroids and/or other cytotoxic agents to successfully treat AHA. Due to the rarity of the disease, most data are derived from case reports or case series rather than large cohort studies. Although the efficacy and safety of these regimens need to be proven by further studies, the existing evidence suggests that they may be viable alternative agents for patients with AHA, especially those with poor prognostic factors and/or relapsed/refractory disease.

Bortezomib

Bortezomib is a proteasome inhibitor originally used as a component of anti-myeloma therapy to induce apoptosis of malignant plasma cells. However, its parallel effects on non-malignant antibody-secreting plasma cells have extended its therapeutic indications to other immune-mediated diseases beyond plasma cell dyscrasias.[25] In AHA, bortezomib was first introduced as a rescue therapy for a patient with relapsed/refractory disease in 2016.[26] After failure to respond to a rituximab-based regimen, subcutaneous bortezomib 1.3 mg/m^2 was administered on days 1, 4, 8, 11, and 21 per 4-week cycle, and resulted in CR after cycle 4. The efficacy and safety of a bortezomib-containing regimen has been systematically investigated in a recent phase 2 trial of the newly diagnosed AHA population in China (n = 30; ClinicalTrials.gov NCT03700229), where intravenous rituximab (375 mg/m^2 given on day 0) combined with subcutaneous bortezomib (1.3 mg/m^2 given on days 1, 4, 8, 11, and 21) was utliized.[27] The CR and PR rates were 77% and 97%, respectively, with a median time to CR of 10.6 weeks and a relapse rate of only

3%. Grade 3-4 infections and neutropenia occurred in 13% and 3% of patients, respectively, while grade 1-2 peripheral neuropathy associated with bortezomib developed in 19% of patients.

Daratumumab

Daratumumab is a first-in-class anti-CD38 mAb primarily used in anti-myeloma therapy. Unlike bortezomib, daratumumab has a unique ability to broadly induce cytotoxicity and apoptosis of not only antibody-secreting plasma cells but also CD38-expressing B-cells and natural killer cells, which are involved in the pathophysiology of autoimmune diseases.[28] The use of low-dose intravenous daratumumab (4-8 mg/kg once a week) in AHA was first described by the Chinese study group to treat patients with relapsed/refractory disease (n = 4).[29] After a median of 17 weekly doses of daratumumab combined with corticosteroids, CR was attained in all patients at a median time of 22.0 weeks. Simultaneously, another study group in Thailand proposed a combined IST regimen using standard-dose intravenous daratumumab (16 mg/kg once a week for 4 weeks), corticosteroids, and cyclophosphamide in a poor-risk patient with newly diagnosed AHA, leading to PR and CR in 4.4 and 9.0 weeks, respectively.[30] With the concomitant use of trimethoprim/sulfamethoxazole and acyclovir prophylaxis recommended for daratumumab-treated patients, no opportunistic infections occurred, despite transient hypogammaglobulinemia and depletion of the B-cell and natural killer cell subpopulations.[29,30] The rapid eradication of high-titer anti-FVIII autoantibodies by the latter regimen may allow early termination of BAs, while the former regimen presents an opportunity to be used in the older more fragile population with relapsed/refractory AHA.

Mycophenolate mofetil

Mycophenolate mofetil (MMF) is an inhibitor of inosine-5'-monophosphate dehydrogenase that targets suppression of guanosine nucleotide synthesis, preferentially in T-cells and B-cells, resulting in the deterioration of cellular immune response and autoantibody production.[31] In most cohort studies, < 5% of patients with AHA was treated with MMF in combination with corticosteroids.[12,19] The largest study, to our knowledge, reported the use of a corticosteroid-MMF regimen in patients with newly diagnosed or relapsed/refractory AHA between 2009 and 2017 in the UK (n = 11).[32] The protocol initiated with MMF 1 g/day in the first week, followed by 2 g/day thereafter. When used as first-line IST, the corticosteroid-MMF combination led to PR in 86% of patients in a median time of 7.5 weeks, while PR was attained in all patients with relapsed/refractory AHA after implementing an MMF-containing regimen for a median time of 3.5 weeks. Infectious complications developed in 36% during the first year of MMF use, but none were associated with mortality. Since the median participant age was 76 years in this study, these findings suggested that the corticosteroid-MMF combination could be a viable alternative to standard IST regimens in managing AHA, particularly for older patients who were unable to tolerate more intensive IST protocols.[3]

Adjunctive intravenous immunoglobulin and plasmapheresis

Theoretically, intravenous immunoglobulin (IVIG) and plasmapheresis may reduce anti-FVIII autoantibodies by neutralizing and removing them from plasma, but their effects are temporary, lasting for a few days to weeks. As suggested by the meta-analysis, IVIG added an uncertain benefit to corticosteroid monotherapy or the corticosteroid-cyclophosphamide combination, with the pooled mean CR rates varying between 33% to 77%.[18] Whereas plasmapheresis in conjunction with IST, with/without autoantibody adsorption using an extracorporeal immunoadsorption column, was reported to rapidly and effectively induce CR (67-88%) in the groups of relapsed/refractory AHA and newly diagnosed AHA with high-titer anti-FVIII autoantibodies.[33,34] However, it remains unclear whether this efficacy is attributable to IST or the passive elimination of anti-FVIII autoantibodies by IVIG

and plasmapheresis. Therefore, the expert consensus recommends against the routine use of IVIG and plasmapheresis for anti-FVIII autoantibody eradication in AHA. However, clinicians might reasonably consider plasmapheresis with/without immunoadsorption to deplete high-titer anti-FVIII autoantibodies in selected patients with life-threatening bleeding inadequately controlled by available hemostatic agents.[3] Appropriate measures to manage the increased risk of bleeding associated with apheresis procedures and central venous catheters should also be concerned.

Deferred immunosuppressive therapy with emicizumab prophylaxis

Emicizumab, a genetically engineered mAb that bispecifically binds to activated factor IX and factor X (FX) resulting in FX activation, has been proven to be an efficacious prophylactic therapy for patients with CHA regardless of anti-FVIII alloantibody status.[35-41] With its FVIII-mimetic function, this non-factor replacement therapy has been adopted for hemostatic management in AHA, aiming to prevent bleeding episodes rather than rescue active bleeding, while deferring and/or reducing the intensity of IST for anti-FVIII autoantibody eradication.[9]

Since 2021-2022, emicizumab prophylaxis has been explored in AHA by 2 prospective cohort studies.[42,43] The Austrian study group first evaluated a protocol of subcutaneous emicizumab 3.0 mg/kg given once a week for 3-4 doses then 1.5 mg/kg once a week thereafter, while rituximab with a short course of corticosteroids (oral prednisolone 1 mg/kg/day for only 1 week followed by tapered withdrawal over 2 weeks) was used as a reduced-intensity IST regimen in patients with AHA (n = 12)[42]. Despite a prolonged median time to PR of 15.0 weeks, all bleeding events were adequately controlled within a median time of 3 days after the first dose of emicizumab, with a median of 5 emicizumab doses required and no additional rFVIIa needed. In parallell, a Japanese study (AGEHA; n = 12) described the use of subcutaneous emicizumab (6.0 mg/kg on day 1 and 3.0 mg/kg on day 2, followed by 1.5 mg/kg once a week) in patients with AHA who received corticosteroid monotherapy or combined IST regimens to eradicate anti-FVIII autoantibodies.[43] All major bleeding events were controlled within the first week of emicizumab prophylaxis, although rFVIIa was still required by 25% of patients to treat non-major bleeding. The median time to PR was 5.1 weeks after concurrent standard-dose IST regimens.

Due to its efficacy in bleeding prevention, irrespective of anti-FVIII autoantibody titers, emicizumab prophylaxis is appropriate in both good-risk and poor-risk patients with AHA while IST is deferred to avoid immediate IST-associated complications in critically ill or frail patients. The concept of deferred IST with emicizumab prophylaxis has been investigated in a phase 2 trial (GTH-AHA-EMI; n = 47) conducted in Germany and Austria.[44] Patients with newly diagnosed AHA received subcutaneous emicizumab based on the protocol used in the AGEHA study until week 12 without IST. Zero bleeds were seen in 70% of patients, with a mean bleeding rate of only 0.04 bleeds per patient per week. However, without IST, anti-FVIII autoantibody titers tended to persist, although a spontaneous PR occurred in 2% of patients. Of patients who received IST after the first 12 weeks of emicizumab prophylaxis, 48% eventually achieved at least PR in the subsequent 12 weeks. The overall survival rate during the study period of 24 weeks was 91%. Two thromboembolic events, including thrombophlebitis and acute ischemic stroke, were reported but were not directly attributed to emicizumab. Compared with the results of the GTH-AH 01/2010 study, the use of emicizumab prophylaxis to defer IST in patients with AHA not only led to the lower rates of rebleeding and fatal infection, but also significantly improved overall survival.[45] Patients on emicizumab prophylaxis might require a shorter length of hospital stay and fewer injections of BAs, contributing to an improved quality of life.

Although emicizumab prophylaxis in AHA can reduce the need for BAs as part of hemostatic treatments, allow attenuation of IST intensity, and serve as a bridging therapy while waiting for clinical stabilization to safely initiate IST or for concurrent IST to take effect, the economic impact of this approach is unknown, especially in low-to-middle-income countries where the use of emicizumab in CHA remains limited.[46,47] Since low-dose emicizumab prophylaxis (≤ 3.0 mg/kg once a month or equivalent doses of emicizumab with/without 1-2 loading doses of 1.0 mg/kg once a week or 2.0 mg/kg every fortnight) has been demonstrated in Asia and Europe to be an effective and affordable regimen for patients with CHA, this modified dosing regimen holds potential for AHA management in resource-constrained settings.[48-55] However, some issues of uncertainty regarding the proposed use of low-dose emicizumab in AHA need to be addressed. First, low-dose emicizumab produces median trough emicizumab plasma levels at steady state of 8.3-20.8 μg/mL in patients with CHA,[49,53,54] lower than those achieved with standard-dose emicizumab in patients with AHA (mean 22.1-37.4 μg/mL).[43,44] Hemostatic efficacy outcomes, such as rebleeding rate, rFVIIa consumption, time to cessation of bleeding, and time to discontinuation of rFVIIa, may not be comparable to those reported in standard-dose emicizumab studies. Second, the steady state emicizumab plasma level is usually reached after 3 doses of low-dose emicizumab, regardless of the use of low-dose loading doses in CHA.[48,49,54] In AHA, however, 2 loading doses of emicizumab (6.0 mg/kg on day 1 and 3.0 mg/kg on day 2) are now recommended during the first week of the standard-dose protocol to expedite achievement of the steady state.[56] Therefore, the low-dose emicizumab protocol for AHA would require modification with a few loading doses at initiation to avoid delaying the prophylactic effect. Third, due to possible inferior efficacy, IST might not be able to be postponed for several weeks with the low-dose emicizumab prophylaxis.[44] Instead, a short deferral period of IST should be reasonable for patients with AHA to start recovering from their critical bleeding. A reduced-dose or standard-dose IST regimen could then be offered to patients as soon as their physical status permits.[56]

To promote equity in AHA management using emicizumab among resource-limited countries, future research to determine the utility of low-dose emicizumab prophylaxis with reduced-dose or standard-dose IST in the AHA population is warranted. The health economic analysis, considering the minimization of the risk of infections and other IST-related complications (primarily recurrent bleeding events), reduction in the use of BAs, and improvement in overall survival, will provide impactful insights to support this low-dose emicizumab approach for AHA.

Conclusions

Eradicating anti-FVIII autoantibodies in AHA under resource constraints requires a strategic approach that balances efficacy, safety, and cost-effectiveness. Although corticosteroid monotherapy remains a cornerstone of first-line IST, combined regimens involving cyclophosphamide and/or rituximab are more effective in achieving the higher CR rates and the lower relapse rates, albeit with increased regimen-related toxicity, in the risk factor-unstratified AHA populations. While tailoring IST based on poor prognostic indicators for response failure to corticosteroid monotherapy, i.e., FVIII:C < 1 IU/dL or anti-FVIII autoantibody titers ≥ 20 BU/mL, aligns with the need for precision in clinical practice and could be considered as an appropriate IST for AHA in resource-limited settings.

Emicizumab represents a significant advancement in AHA management by allowing for the deferral of IST and the reduction of IST intensity, making it a valuable option for older patients with poor functional status at the time of AHA diagnosis. The concept of deferred IST with emicizumab prophylaxis has shown promising results in reducing the rebleeding rates, decreasing the

use of BAs, and improving overall survival. However, the economic impact and feasibility of this approach in low-to-middle-income countries deserve further investigation. The adaptation of low-dose emicizumab prophylaxis used in patients with CHA, potentially combined with loading doses, offers a feasible alternative protocol for countries with significant budget constraints. Future studies should focus on optimizing these protocols and conducting health economic analyses to support their implementation.

In conclusion, the management of AHA in resource-limited settings necessitates innovative and flexible approaches that maximize therapeutic outcomes while minimizing costs and adverse effects. Collaboration and continued research are essential to improve the equity and effectiveness of AHA care globally.

Acknowledgements

The authors appreciate the Thai Society of Hematology for its continuous efforts over the past 3 decades to domestically promote the standard of care to the hemophilia commutinity in Thailand. This model may provide an opportunity for other low-to-middle-income countries in southeast Asia and other regions to develop and/or improve their local hemophilia care systems. We would also like to extend our gratitude to Professor Ampaiwan Chuansumrit, MD, and Professor Darintr Sosothikul, MD, for their significant contributiions to low-dose emicizumab prophylaxis in the CHA population, which could potentially be a feasible therapeutic approach for AHA.

Author contributions

C.M. conceptualized the scope of the review article, searched the literature, extracted and interpreted data, and drafted the manuscript; P.E. and N.S.K. gave advice on the deferred IST with emicizumab prophylaxis and the proposed use of low-dose emicizumab in AHA, critically reviewed and edited the manuscript; all authors read and approved the final manuscript.

Disclosures

P.E. has received the Access to Insight Basic Research Grant from Novo Nordisk Inc. and has been a consultant for Genentech Inc. N.S.K. has been a consultant for BioMarin Pharmaceutical Inc., uniQure Inc., CSL Behring LLC, and Centessa Pharmaceuticals LLC, and has chaired an IIS grants review panel for Novo Nordisk Inc. C.M. stated that there are no interests that might be perceived as posing a conflict or bias.

References

1. *Ma AD, Carrizosa D. Acquired factor VIII inhibitors: pathophysiology and treatment. Hematol Am Soc Hematol Educ Program. 2006;2006:432-7.*
2. *Kruse-Jarres R, Kempton CL, Baudo F, Collins PW, Knoebl P, Leissinger CA, et al. Acquired hemophilia A: updated review of evidence and treatment guidance. Am J Hematol. 2017;92:695-705.*
3. *Tiede A, Collins P, Knoebl P, Teitel J, Kessler C, Shima M, et al. International recommendations on the diagnosis and treatment of acquired hemophilia A. Haematologica. 2020;105:1791-801.*
4. *Hay CR, Negrier C, Ludlam CA. The treatment of bleeding in acquired haemophilia with recombinant factor VIIa: a multicentre study. Thromb Haemost. 1997;78:1463-7.*
5. *Tiede A, Worster A. Lessons from a systematic literature review of the effectiveness of recombinant factor VIIa in acquired haemophilia. Ann Hematol. 2018;97:1889-901.*
6. *Sallah S. Treatment of acquired haemophilia with factor eight inhibitor bypassing activity. Haemophilia. 2004;10:169-73.*
7. *Baudo F, Collins P, Huth-Kühne A, Lévesque H, Marco P, Nemes L, et al. Management of bleeding in acquired hemophilia A: results from the European Acquired Haemophilia (EACH2) Registry. Blood. 2012;120:39-46.*
8. *Kruse-Jarres R, St-Louis J, Greist A, Shapiro A, Smith H, Chowdary P. et al. Efficacy and safety of OBI-1, an antihaemophilic factor VIII (recombinant), porcine sequence, in subjects with acquired haemophilia A. Haemophilia. 2015;21:162-70.*
9. *Tiede A, Kemkes-Matthes B, Knöbl P. Should emicizumab be used in patients with acquired hemophilia A? J Thromb Haemost. 2021;19:637-44.*
10. *Collins PW, Hirsch S, Baglin TP, Dolan G, Hanley J, Makris M, et al. Acquired hemophilia A in the United Kingdom: a 2-year national surveillance study by the United Kingdom Haemophilia Centre Doctors' Organisation. Blood. 2007;109:1870-7.*
11. *Collins P, Baudo F, Knoebl P, Lévesque H, Nemes L, Pellegrini F, et al. Immunosuppression for acquired hemophilia A: results from the European Acquired Haemophilia Registry (EACH2). Blood. 2012;120:47-55.*

12. Schep SJ, van Dijk WEM, Beckers EAM, Meijer K, Coppens M, Eikenboom J, et al. Treatment of acquired hemophilia A, a balancing act: results from a 27-year Dutch cohort study. Am J Hematol. 2021;96:51-9.
13. Mingot-Castellano ME, Pardos-Gea J, Haya S, Bastida-Bermejo JM, Tàssies D, Marco-Rico A, et al. Management of acquired hemophilia A: results from the Spanish registry. Blood Adv. 2021;5:3821-9.
14. Tiede A, Klamroth R, Scharf RE, Trappe RU, Holstein K, Huth-Kühne A, et al. Prognostic factors for remission of and survival in acquired hemophilia A (AHA): results from the GTH-AH 01/2010 study. Blood. 2015;125:1091-7.
15. Sun B, Xue F, Feng Y, Sun J, Yu Z, Hou M, et al. Outcome of CARE: a 6-year national registry of acquired haemophilia A in China. Br J Haematol. 2019;187:653-65.
16. Wongrakpanich S, Uaprasert N, Akkawat B, Nanakhon T, Rojnuckarin P. Acquired factor VIII inhibitor in King Chulalongkorn Memorial Hospital. J Hematol Transfus Med. 2012;22:195-201.
17. Chai-Adisaksopha C, Rattarittamrong E, Norasetthada L, Tantiworawit A, Nawarawong W. Younger age at presentation of acquired haemophilia A in Asian countries: a single-centre study and systematic review. Haemophilia. 2014;20:e205-10.
18. Rungjirajittranon T, Suwanawiboon B, Nakkinkun Y, Leelakanok N, Kaokunakorn T, Chinthammitr Y, et al. First-line immunosuppressive therapies for acquired hemophilia A: a 25-year cohort experience and network meta-analysis. Thromb Res. 2024;241:109067.
19. Borg JY, Guillet B, Le Cam-Duchez V, Goudemand J, Lévesque H, SACHA Study Group. Outcome of acquired haemophilia in France: the prospective SACHA (Surveillance des Auto antiCorps au cours de l'Hémophilie Acquise) registry. Haemophilia. 2013;19:564-70.
20. Sperr WR, Lechner K, Pabinger I. Rituximab for the treatment of acquired antibodies to factor VIII. Haematologica. 2007;92:66-71.
21. Lévesque H, Viallard JF, Houivet E, Bonnotte B, Voisin S, Le Cam-Duchez V, et al. Cyclophosphamide vs rituximab for eradicating inhibitors in acquired hemophilia A: a randomized trial in 108 patients. Thromb Res. 2024;237:79-87.
22. Wang P, Zhou R, Xue F, Zhou H, Bai J, Wang X, et al. Single-dose rituximab plus glucocorticoid versus cyclophosphamide plus glucocorticoid in patients with newly diagnosed acquired hemophilia A: a multicenter, open-label, randomized noninferiority trial. Am J Hematol. 2024;99:28-37.
23. Simon B, Ceglédi A, Dolgos J, Farkas P, Gaddh M, Hankó L, et al. Combined immunosuppression for acquired hemophilia A: CyDRi is a highly effective low-toxicity regimen. Blood. 2022;140:1983-92.
24. Dobbelstein C, Moschovakis GL, Tiede A. Reduced-intensity, risk factor-stratified immunosuppression for acquired hemophilia A: single-center observational study. Ann Hematol. 2020;99:2105-12.
25. Ratnasingam S, Walker PA, Tran H, Kaplan ZS, McFadyen JD, Tran H, et al. Bortezomib-based antibody depletion for refractory autoimmune hematological diseases. Blood Adv. 2016;1:31-5.
26. McFadyen JD, Tran H, Kaplan ZS. Factor VIII inhibitor eradication with bortezomib in acquired haemophilia A. Br J Haematol. 2017;178:986-7.
27. Cai H, Cao X, Wang S, Zhao Y, Li J, Zhu TN. Rituximab and bortezomib for patients with newly diagnosed acquired heamophilia: single arm, single center, prospective phase 2 study. Blood. 2022;140(Suppl 1):2715-6.
28. Markmann C, Bhoj VG. On the road to eliminating long-lived plasma cells- "are we there yet?" Immunol Rev. 2021;303:154-67.
29. Liu W, Liu J, Xue F, Yang R, Zhang L. Anti-CD38 antibody for refractory acquired hemophilia A. J Thromb Haemost. 2023;21:1515-8.
30. Moonla C, Polprasert C, Krittikarux S, Cheerasiri N, Akkawat B, Rojnuckarin P, Uaprasert N. Adjunctive daratumumab can induce rapid remission in acquired haemophilia A with poor prognostic markers. Haemophilia. 2023;29:1649-52.
31. Allison AC, Eugui EM. Mycophenolate mofetil and its mechanisms of action. Immunopharmacology. 2000;47(2-3):85-118.
32. Obaji S, Rayment R, Collins PW. Mycophenolate mofetil as adjunctive therapy in acquired haemophilia A. Haemophilia. 2019;25:e59-e65.
33. Freedman J, Rand ML, Russell O, Davis C, Cheatley PL, Blanchette V, Garvey MB. Immunoadsorption may provide a cost-effective approach to management of patients with inhibitors to FVIII. Transfusion. 2003;43:1508-13.
34. Zeitler H, Ulrich-Merzenich G, Hess L, Konsek E, Unkrig C, Walger P, et al. Treatment of acquired hemophilia by the Bonn-Malmo Protocol: documentation of an in vivo immunomodulating concept. Blood. 2005;105:2287-93.
35. Callaghan MU, Negrier C, Paz-Priel I, Chang T, Chebon S, Lehle M, et al. Long-term outcomes with emicizumab prophylaxis for hemophilia A with or without FVIII inhibitors from the HAVEN 1-4 studies. Blood. 2021;137:2231-42.
36. Oldenburg J, Mahlangu JN, Kim B, Schmitt C, Callaghan MU, Young G, et al. Emicizumab prophylaxis in hemophilia A with inhibitors. N Engl J Med. 2017;377:809-18.
37. Young G, Liesner R, Chang T, Sidonio R, Oldenburg J, Jiménez-Yuste V, et al. A multicenter, open-label phase 3 study of emicizumab prophylaxis in children with hemophilia A with inhibitors. Blood. 2019;134:2127-38.
38. Mahlangu J, Oldenburg J, Paz-Priel I, Negrier C, Niggli M, Mancuso ME, et al. Emicizumab prophylaxis in patients who have hemophilia A without inhibitors. N Engl J Med. 2018;379:811-22.
39. Pipe SW, Shima M, Lehle M, Shapiro A, Chebon S, Fukutake K, 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:e295-e305.
40. Yang R, Wang S, Wang X, Sun J, Chuansumrit A, Zhou J, et al. Prophylactic emicizumab for hemophilia A in the Asia-Pacific region: a randomized study (HAVEN 5). Res Pract Thromb Haemost. 2022;6:e12670.

41. *Négrier C, Mahlangu J, Lehle M, Chowdary P, Catalani O, Bernardi RJ, et al. Emicizumab in people with moderate or mild haemophilia A (HAVEN 6): a multicentre, open-label, single-arm, phase 3 study. Lancet Haematol. 2023;10:e168-77.*
42. *Knoebl P, Thaler J, Jilma P, Quehenberger P, Gleixner K, Sperr WR. Emicizumab for the treatment of acquired hemophilia A. Blood. 2021;137:410-9.*
43. *Shima M, Amano K, Ogawa Y, Yoneyama K, Ozaki R, Kobayashi R, et al. A prospective, multicenter, open-label phase III study of emicizumab prophylaxis in patients with acquired hemophilia A. J Thromb Haemost. 2023;21:534-45.*
44. *Tiede A, Hart C, Knöbl P, Greil R, Oldenburg J, Sachs UJ, et al. Emicizumab prophylaxis in patients with acquired haemophilia A (GTH-AHA-EMI): an open-label, single-arm, multicentre, phase 2 study. Lancet Haematol. 2023;10:e913-21.*
45. *Hart C, Klamroth R, Sachs UJ, Greil R, Knoebl P, Oldenburg J, et al. Emicizumab versus immunosuppressive therapy for the management of acquired hemophilia A. J Thromb Haemost. 2024: S1538-7836(24)00368-4. doi: 10.1016/j.jtha.2024.06.010. [Epub ahead of print]*
46. *Moonla C, Sosothikul D, Pongtanakul B, Suwanawiboon B, Traivaree C, Natesirinilkul R, et al. Practices and challenges for hemophilia management under resource constraints in Thailand. Orphanet J Rare Dis. 2023;18:110.*
47. *Sosothikul D, Moonla C. Paradigm shifts in haemophilia A therapy with emicizumab prophylaxis in Asia. Ann Acad Med Singap. 2023;52:556-8.*
48. *Chuansumrit A, Sirachainan N, Jaovisidha S, Jiravichitchai T, Kadegasem P, Kempka K, et al. Effectiveness of monthly low dose emicizumab prophylaxis without 4-week loading doses among patients with haemophilia A with and without inhibitors: a case series report. Haemophilia. 2023;29:382-5.*
49. *Kessakorn N, Srichumpuang C, Moonla C, Sosothikul D. Low-dose emicizumab versus low-dose factor VIII secondary prophylaxis for noninhibitor hemophilia A patients with severe bleeding phenotype. Paper presented at: The International Society on Thrombosis and Haemostasis 2024 Congress; 2024 Jun 22-26; Bangkok, Thailand.*
50. *Shima M, Nagao A, Taki M, Matsushita T, Oshida K, Amano K, 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;27:81-9.*
51. *Lehtinen AE, Lassila R. Do we need all that emicizumab? Haemophilia. 2022;28:e53-5.*
52. *Tang ASO, Ko CT, Saari Z, Selvaratnam V, Chew LP, Sathar J. Efficacy of reduced-dose emicizumab in hemophilia A with inhibitors: real world experience in Malaysia. Hemasphere. 2023;7(Suppl 3):e269464e.*
53. *Bansal S, Donners AAMT, Fischer K, Kshirsagar S, Rangarajan S, Phadke V, et al. Low dose emicizumab prophylaxis in haemophilia A patients: a pilot study from India. Haemophilia. 2023;29:931-4.*
54. *Patil R, Shanmukhaiah C, Gogtay NJ, Pandey P, Patil K, Jijina F, Madkaikar M. Low-dose emicizumab prophylaxis in patients with severe hemophilia A: a retrospective study bringing new hope for our patients. J Thromb Haemost. 2024;22:1024-30.*
55. *Mannucci PM, Hermans C. Low-dose emicizumab for more equitable access to prophylaxis in resource limited countries. Haemophilia. 2024;30:575-6.*
56. *Pfrepper C, Klamroth R, Oldenburg J, Holstein K, Eichler H, Hart C, et al. Emicizumab for the treatment of acquired hemophilia A: consensus recommendations from the GTH-AHA Working Group. Hamostaseologie. 2023. doi: 10.1055/a-2197-9738. [Epub ahead of print]*