

Paradigm shifts in haemophilia A therapy with emicizumab prophylaxis in Asia

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Over the past decade, the development of emicizumab, the first-in-class factor VIII (FVIII)-mimetic monoclonal antibody bispecific to activated factor IX and factor X, has ushered in a significant revolution in non-factor replacement therapy for patients with congenital FVIII deficiency or haemophilia A (HA). This groundbreaking therapy has been unequivocally supported by a series of international, multicentre, phase 3 studies, conclusively demonstrating that subcutaneous emicizumab prophylaxis can effectively and safely promote haemostasis to prevent bleeds in both paediatric and adult patients with severe or non-severe HA, with or without FVIII inhibitors.^{1,2} Due to a long elimination half-life of 4–5 weeks leading to a stabilised in vivo FVIII-like activity of 20–30 IU/dL, the annualised bleeding rate (ABR) could be significantly reduced to 1.4 for treated bleeds and 2.6 for all bleeds after receiving 4 loading doses (3.0 mg/kg once a week) followed by maintenance doses (1.5 mg/kg once a week, 3.0 mg/kg every 2 weeks, or 6.0 mg/kg every 4 weeks) of emicizumab for a median follow-up time of 120 weeks in the HAVEN 1–4 studies.¹ Remarkably, 90% of patients eventually achieved 0 bleeds with 95% resolution of target joints. Furthermore, the less frequent subcutaneous injections of emicizumab meaningfully contributed to an improvement in health-related quality of life and a reduction in caregiver burden for patients with HA, particularly those with difficult venous access. Given its promising efficacy, especially in the inhibitor group for which factor replacement therapy with FVIII concentrate is contraindicated, emicizumab prophylaxis has swiftly emerged as one of the standard HA treatments worldwide, regardless of FVIII inhibitor status.

Concerning geographical disparities in Asian countries, a phase 3 study (HAVEN 5) enrolling patients aged ≥ 12 years with severe HA without FVIII inhibitors or severe/moderate HA with FVIII

inhibitors exclusively from China, Malaysia and Thailand was separately conducted. Despite 74% of patients having target joints—higher than 61% observed in the HAVEN 1–4 studies—prophylaxis with standard-dose emicizumab for at least 24 weeks still led to excellent bleed control with the ABR of 1.0 for treated bleeds, as well as 0 treated bleeds in 61% of patients.³ Aligning with the results from phase 3 studies, 2 retrospective studies from China and South Korea similarly showed substantial reductions in the ABR after using standard-dose emicizumab prophylaxis among paediatric and adult patients with severe/moderate HA. Zero bleeds were also achievable in 46–56% of patients in real-world settings.^{4,5} As it is commonly known that several HA communities in Asia had experienced limited access to FVIII prophylaxis and treatments for HA with FVIII inhibitors,⁶ resulting in a greater burden of haemophilic arthropathy and bleeding complications, these haemophilia-related morbidities can be overcome, and currently unmet needs in HA therapy may be fulfilled with emicizumab prophylaxis.

In Singapore, where 18% of patients with HA developed FVIII inhibitors, Lee et al. reported the utility of standard-dose emicizumab prophylaxis in 15 paediatric and 3 adult patients with severe HA without FVIII inhibitors or HA of any severity with FVIII inhibitors, since the introduction of emicizumab in September 2018.⁷ At a median follow-up time of 22 months, the median ABR of 4.5 (3.0 in the non-inhibitor and 5.5 in the inhibitor groups) before switching treatments to emicizumab prophylaxis was absolutely suppressed to 0 in both presence and absence of FVIII inhibitors. Despite a low prevalence of target joints (11%) and a modest initial rate of 0 bleeds (22%), 0 bleeds were further induced to 83% overall and 75% in the inhibitor group. Interestingly, real-world data in a subgroup of patients aged < 2 years were also described;

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2 out of 4 patients started emicizumab prophylaxis before 1 year of age, beyond the age range of participants in the HAVEN 2 study, while a phase 3 study in the infant population (HAVEN 7; NCT04431726) is still ongoing.¹ In the Singaporean cohort, 0 bleeds were achieved in 75% of infants and toddlers with HA at a median time of 18 months of emicizumab use. On safety profiles, the emicizumab regimen was well-tolerated in all age groups and did not contribute to any thrombotic adverse events.

In addition to validating its efficacy and safety in bleed control, Lee et al. demonstrated the use of emicizumab prophylaxis during surgical interventions and immune tolerance induction (ITI) for FVIII inhibitor eradication.⁷ With additional doses of FVIII concentrate or recombinant activated factor VII in the perioperative periods, all procedures were successfully performed without bleeding or thrombotic complications. In 7 patients with high-titre FVIII inhibitors who underwent low-dose (86%) or high-dose (14%) ITI using FVIII concentrate, inhibitor negativity could be induced in 43% of patients without any safety concerns while on concurrent emicizumab prophylaxis. These real-world experiences provided supporting evidence for the results of the HAVEN 1–4 studies and a previous study of the ITI Atlanta protocol concomitantly using emicizumab for bleed control.^{1,8} The positive outcomes suggested that standard-dose emicizumab is a valuable therapeutic option to prevent bleeds, either as a regular prophylaxis, during surgical procedures, or as an adjunct to the ITI regimen, for patients with severe or non-severe HA in Asia.

Despite its strong potential, budget constraints can be a major limitation in the implementation of standard-dose emicizumab prophylaxis in real-world practice among developing Asian countries.⁶ Therefore, to be more economically compatible with local healthcare policy, the concept of reduced-dose or low-dose emicizumab prophylaxis (1.0–3.0 mg/kg/month) has been introduced.^{9–11} In a case series from Malaysia, although switching emicizumab prophylaxis from standard-dose to reduced-dose regimens slightly increased bleeding rates, 44% of patients maintained 0 bleeds during a median follow-up time of 198 weeks.⁹ In a study from India that evaluated the efficacy and safety of low-dose emicizumab prophylaxis in severe HA patients, with or without FVIII inhibitors, who were formerly treated with a standard-dose regimen or emicizumab-naïve, at a median follow-up time of 52 weeks, no treated bleeds or thrombotic complications were reported.¹⁰ Similarly, in another study in Thailand, even without 4 loading doses, emicizumab-naïve severe/moderate HA patients

with or without FVIII inhibitors still benefited from low-dose emicizumab prophylaxis, with 82% reduction in ABR from a median of 27.0 at baseline to 4.0 after prophylaxis for 1 year, with 0 bleeds achieved in 33% of patients.¹¹

For a comprehensive comparison of various emicizumab regimens among Asian studies, PubMed and Embase were systematically searched from database inception to 12 September 2023, for studies in Asian countries reporting haemophilia-related clinical outcomes in patients with severe and/or non-severe HA receiving emicizumab prophylaxis. Of 58 unique records identified by the search terms “emicizumab” and “Asia”, 8 studies were included after screening titles, abstracts, and full texts.^{3–5,9–13} Including the latest study by Lee et al.,⁷ a total of 9 eligible studies represented 171 patients with HA. Standard-dose and low-dose emicizumab regimens were applied in 6 and 4 studies, respectively. Although the median ABR during low-dose emicizumab tended to be higher than those during standard-dose emicizumab prophylaxis, a low-dose regimen significantly provided better bleed control than before or without emicizumab use.^{10–12} No new safety profiles were documented in both studies of standard-dose and low-dose regimens. Based on these accumulative data, low-dose emicizumab prophylaxis could be an alternative HA treatment where the accessibility to a standard-dose regimen was limited. However, due to the small number of participants in most studies, further multicentre clinical trials or well-designed prospective studies are warranted to establish more robust evidence on the efficacy of low-dose emicizumab, compared to standard-dose emicizumab regimens.

In conclusion, emicizumab has globally shifted paradigms of prophylactic therapy for patients with HA, particularly those with FVIII inhibitors who are at the highest risk of bleeding, associated with increased morbidity and mortality. The current evidence, including, to our knowledge, the largest-to-date real-world study in Asia by Lee et al.,⁷ confirms that weekly to monthly subcutaneous injections of emicizumab can contribute to effective bleed control and increase the possibility of achieving 0 or near 0 bleeds for patients with HA of any severity or FVIII inhibitor status. In Asian countries with significant budget constraints, a low-dose emicizumab regimen may be alternatively considered according to local policy and budget allotment, while its overall efficacy is anticipated. With factor replacement therapy using FVIII concentrate and non-factor replacement therapy using emicizumab, the evolution of HA therapy helps optimise treatment outcomes and promote a better quality of life for patients with HA.

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Data availability

The supporting data are available from the corresponding author upon reasonable request.

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