

Leave no one behind: Optimal Care of all Patients with Haemophilia A.

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Background: Haemophilia is an inherited bleeding disorder due to failure of thrombin generation resulting from clotting factor deficiency. In haemophilia A, the deficient factor is Factor VIII due to mutations in the F8 gene. In the past several decades, we have seen an unprecedented evolution of therapies for managing haemophilia A (Mahlangu, 2022). These have included blood and blood products to plasma-derived concentrate, recombinant concentrate, concentrate with improved pharmacokinetics and, more recently, non-replacement therapies. Notwithstanding these advances in treatments, patients with haemophilia A (PwHA) remain with several unmet needs.

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Unmet needs in haemophilia

The recent CHES II study indicates that PwHA has problem joints across all severities of haemophilia. This study included 258 PwHA, of which 47%, 39% and 20% of patients with severe, moderate and mild haemophilia had problem joints, respectively (Gringeri et al., 2014). It may not be comforting that both severe and moderate haemophilia were affected, suggesting that converting a patient from extreme to moderate is not an ideal goal. The reason for this study's high bleed rate was that only 60%, 7% and 5% of patients with severe, moderate and mild disease were on prophylaxis. Naturally, in haemophilia, bleeding leads to joint damage and arthropathy. In the HEMOCARE study, the authors quantified the extent of arthropathy in PwHA with and without inhibitors across all age groups living in middle-low-income countries (Gupta et al., 2019). Not surprisingly, there was a high burden of musculoskeletal disease in the 127 study participants. Joint damage was across all severities of haemophilia with and without inhibitors. No joint was spared from the effects of repeated bleeds and their consequences. When patients are followed longitudinally, it appears there is no mitigation for joint damage deterioration. This was shown elegantly in the AHEAD study, where there was no change in the mean number of bleeds when patients were followed up for three years (Kruse-Jarres et al., 2019). Most worrying was the comparison of those on prophylaxis and episodic treatment, which revealed very little difference in the bleed rates. Part of the challenge is that not only are people not receiving prophylaxis which is the current standard of care, but they are also not getting prophylaxis using the correct regimens or prophylactic agents.

Goals of haemophilia care

The goals of haemophilia care have been evolving, from keeping patients alive to achieving normal haemostasis in the future (Skinner et al., 2020). The 2020 World Federation of Haemophilia Guideline of haemophilia management has not only declared prophylaxis as the new global standard of care but has also outlined the goals of prophylaxis

(Srivastava et al., 2020). In this guideline, effective prevention is expected to allow patients to live active lives and achieve a quality of life comparable to that of non-haemophilia individuals. The guideline recommends individualising prophylaxis, considering the patient's bleeding phenotype, joint status, individual pharmacokinetics, and patient activities. The guideline makes a clear distinction between severe bleeding phenotype and disease categorisation. All efforts should address the severe bleeding phenotype irrespective of the disease category. Finally, the guideline recommends that prophylaxis be started early to prevent joint damage. This recommendation is supported by the joint outcome study conducted in the USA from 1999 to 2010 (Manco-Johnson et al., 2017). In this study, children who began prophylaxis after age 6 had higher rates of joint damage than those who started prevention before age 2.

Potential mitigating measures and promising outcomes

The prophylaxis goals are achievable through several strategies. Firstly, we now have a variety of therapeutic agents we use, including products, recombinant products and non-replacement therapies (Mahlangu, 2022). The estimated global FVIII consumption in 2020 was 12 billion units. It is a fact that these units are accessible to all PwHA on a fair and equitable basis, and estimates are that more than 70% of the global haemophilia population does not have access to treatment. We now have several dosing regimens to choose from for our patients, including regimens dosing by intensity or class of therapeutic agent. In the former category are high-dose, intermediate dose, and regimens we can tailor according to individual needs (Fischer et al., 2002; Gouider et al., 2017; Nilsson et al., 1992; Verma et al., 2016). The agents used include standard half-life, extended half-life, and non-factor therapies, many of which can achieve steady-state haemostasis. Despite the many challenges with faithful haemophilia care, significant progress has been made. Many patients receiving non-replacement treatments show substantial improvement in the quality of their lives compared to those receiving

replacement therapies (Kenet et al., 2021) . Recent data from emicizumab indicate that patients have increased school attendance when receiving emicizumab prophylaxis.

Data from the four Phase 3 HAVEN programs indicate that target joint resolution is high in patients receiving non-replacement therapy prophylaxis. In these four studies, the target joint resolution had a mean of 99% (Callaghan et al., 2021) . In these studies, the bleeds rates were low across paediatric, adolescent and adult age groups. Over a long follow-up period of four years, the mean annualised bleed rate was less than one across three dosing regimens.

Barriers to optimal care of PwHA

The most significant barrier to optimal haemophilia care is the lack of access to treatment (Srivastava et al., 2020) . In countries with access to therapeutic agents, there are many barriers to the universal adoption of prophylaxis. These barriers include patient-related factors and healthcare provider factors. Patient-related factors include 1) perceived burden of prophylaxis, 2) challenges of home administration of prophylaxis, 3) interference of prophylaxis with patient lifestyle, and 4) lack of understanding of the impact of episodic treatment of progression of arthropathy. Healthcare providers also contribute to poor updates of prophylaxis, and reasons include 1) not recognising that prophylaxis should be the standard of care for all severe bleeding phenotypes, 2) the perception that PwHA may not need prophylaxis, 3) the dilemma of competing for resource allocation. Additionally, many PwHA have little involvement in their treatment decisions. In the CHES II study, the level of participation of patients in their therapeutic decision-making remains below 35%. This may, in part, be because shared decision-making has yet to be universally adopted as a tool to facilitate participation in their care (Hermans et al., 2022) . Shared decision-making requires that the team take into account several factors when making therapeutic decisions, and these include 1) patient bleeding phenotype, 2) lifestyle, 3) venous access, 4) joint status, 5) treatment adherence, and 6) joint status (Hermans et al., 2022) .

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