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CLINICAL UPDATE

Prophylaxis is the new standard of care in patients with haemophilia

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Randomised controlled clinical trial evidence on prophylaxis as optimal care for patients with haemophilia was generated more than a decade ago. However, this knowledge has not translated into clinical practice in South Africa (SA) owing to many barriers to prophylaxis. These include the high treatment burden imposed by prophylaxis (frequent injections two to four times a week), the need for intravenous access to administer replacement clotting factor therapies, and the higher volume of clotting factor required compared with episodic treatment. The recently introduced non-factor therapies in haemophilia care have addressed many of these barriers. For example, emicizumab, which is currently the only globally approved non-factor therapy, can be administered subcutaneously less frequently (weekly, fortnightly or every 4 weeks) and has led to global adoption of prophylaxis as the standard of care in haemophilia by the bleeding disorders community. Haemophilia A is the most prevalent clotting factor deficiency in SA, with >2 000 people diagnosed to date. However, only a few of these patients are currently on prophylaxis. In this 'In Practice' article, we review the rationale for prophylaxis, outline its goals and benefits, and provide evidence-based guidance on which haemophilia patients should be prioritised for emicizumab prophylaxis. This consensus guidance facilitates the adoption of prophylaxis as a national policy and the new standard of care in haemophilia in SA.

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Inherited bleeding disorders: Epidemiology and clinical phenotype

Inherited bleeding disorders are diverse in aetiology, clinical presentation and epidemiology. They include those caused by lack of Von Willebrand factor, factor VIII (FVIII) deficiency (haemophilia A), and factor IX (FIX) deficiency (haemophilia B).[1] The causative gene mutations in these conditions are well characterised, and they can be inherited or acquired following spontaneous mutations. Mutation prevalence is the same globally, irrespective of race, ethnicity, geographical location or socioeconomic status.[2]

Of the 3 142 patients diagnosed with inherited clotting factor deficiencies in South Africa (SA), 1 986 have haemophilia A, 379 have haemophilia B, 659 have Von Willebrand disease, and 118 have other rare bleeding disorders (factor VII, X and XI deficiencies).[3] The majority of these patients (85%) are managed in the public sector by 22 haemophilia treatment centres across the nine provinces. The clinical phenotype of clotting factor deficiency is characterised by spontaneous or trauma-induced bleeding, with predominantly mucocutaneous bleeding in Von Willebrand disease and haemarthroses in the haemophilias. Bleeding and bleed-related complications are lifelong, with consequent characteristic haemophilic arthropathies, reduced quality of life and reduced life expectancies of patients with these conditions.

Treatment of haemophilia A

The current globally accepted standard of care in haemophilia A and all other inherited bleeding disorders is intravenous replacement of the missing clotting factor.[1] However, the therapeutic tools used in replacement have evolved over several decades, from blood and blood products to plasma-derived clotting factor concentrates, followed more recently by recombinant clotting factor products with improved pharmacokinetics.[4] While there are many benefits to using replacement therapies, they also pose several challenges. The challenges of administering them intravenously are obvious. In addition, their use is associated with the development of anti-clotting factor neutralising antibodies (inhibitors), which occur in up to 30% of patients with haemophilia A.[5] As a result, non-factor therapies have evolved to address these challenges.

While several non-factor therapies are currently in various stages of clinical development,[6] emicizumab has completed five phase 3 studies and is currently registered in >100 countries, including SA.[7] Emicizumab is a bispecific monoclonal antibody that combines activated factor IX and factor X to form a tenase coagulation complex. It essentially performs the same function as the missing FVIII in haemophilia A.[8] Emicizumab is given subcutaneously and can be used for all age groups. Its maintenance dose is the same whether administered weekly, fortnightly or every 4 weeks, irrespective of the presence of inhibitors. The safety and efficacy profile of emicizumab has been established in several completed phase 3 studies[8-10] and real-world experience studies.[11-13]

Emicizumab and other replacement therapies have transformed the therapeutic landscape in haemophilia A. In countries where the barriers to prophylaxis implementation using intravenous replacement are significant, these newer agents create the possibility of changing treatment strategies from a reactive (episodic treatment used to treat a bleed) to a proactive approach (the prophylaxis used to prevent bleeds).

Prophylaxis as the new standard of care

Prophylaxis is the regular administration of a haemostatic agent or agents that safely, effectively and conveniently prevent bleeding while allowing persons with haemophilia to live active lives.[14,15] It is distinct from episodic or on-demand treatment, which replaces the missing clotting factor after a bleeding event.[14] The latest World Federation of Haemophilia (WFH) 2020 haemophilia treatment guideline has recommended that prophylaxis is the new global standard of care for all patients with haemophilia.[1] The superiority of prophylaxis was first demonstrated in a randomised control study by Manco-Johnson *et al*.[16] published in 2007, and their findings have been supported by clinical studies and real-world experience studies.[17,18] Prophylaxis is further supported by several studies conducted in five low- to middle-income countries which showed that giving patients FVIII prophylaxis at 10 - 15 IU/kg two to three times a week or FIX prophylaxis at 10 - 15 IU/kg twice a week resulted in a clinically significant reduction in bleed rates compared with episodic treatment.[19-24] Prophylaxis is therefore the recommended standard of care, even in resource-constrained settings.

The WFH 2020 haemophilia treatment guideline[1] further recommends: (*i*) early initiation of long-term prophylaxis with standard or extended half-life FVIII (or other haemostatic agents) before the onset of joint disease and ideally at age <3 years; (*ii*) that patients with severe haemophilia A receive individualised prophylaxis sufficient to prevent bleeds at all times; and (*iii*) pharmacokinetic monitoring for patients with haemophilia to maintain a trough level higher than the previously recommended 1%. These recommendations align with modern personalised patient care[25] and aim to address the under-recognised and poorly managed subclinical bleeds seen in many patients on standard prophylaxis regimens.

The therapeutic goal of prophylaxis is to prevent spontaneous bleeding with consequent preservation of joint health.[16] Haemophilia patients with healthy joints can undertake normal activities of daily living and live relatively normal lives.[26] The long-term benefits of prophylaxis include less arthropathy, less disability, and improved quality of life.[27,28] However, the goals and benefits of prevention may not be achievable if the barriers are not identified and removed. Of the many obstacles to prophylaxis with factor concentrates, the two most noteworthy are: (*i*) the high treatment burden imposed by frequent intravenous administration of factor; and (*ii*) the cost of prophylaxis. For example, a child receiving prophylaxis three times a week will require 156 injections per year if they are 100% compliant for 52 weeks.[4] Unfortunately, intravenous access is difficult in many patients with haemophilia, with limited veins available, and exacerbated by frequent access attempts at venepuncture with consequent physical and emotional scarring at each visit. Paediatric patients with intravenous access devices are a particular challenge as these devices are often thrombosed or become infected, leading to hospitalisation, interruption of the prophylaxis regimen, and long-term complications.[1] The requirement for regular venous access and the associated treatment burden has been removed by subcutaneously administered emicizumab.[29]

The cost of prophylaxis has made it inaccessible and unaffordable to many patients with haemophilia worldwide, particularly those living in resource-constrained health systems.[3] The amount of clotting factor required is 2 000 - 4 000 IU/kg/year for the intermediate-dose regimen and >4 000 IU/kg/year for the high-dose regimen.[30,31] In this context, low-dose regimens for replacement therapies were developed, requiring 1 000 IU/kg/year for prophylaxis. While it is now accepted that the low-dose regimens will not prevent the progression of arthropathy, they at least allow prophylaxis and reduce spontaneous bleeds. The cost of prophylaxis with emicizumab is comparable to or less than the cost of treating bleeds with bypassing agents in patients with inhibitors.[32,33] However, emicizumab may

remain unaffordable for haemophilia A patients without inhibitors and for patients in resource-constrained settings for a significant length of time. In these settings, cost-effective guidance on who should be prioritised for emicizumab prophylaxis would be helpful.

Evidence-based consensus statements on which patients with haemophilia A should be prioritised for emicizumab prophylaxis

A group of haemophilia experts comprising haematologists, physicians and paediatricians treating patients with haemophilia, of all age groups, and a haemophilia nurse and a patient representative from SA, met several times to formulate an evidence-based consensus statement to guide the choice of patients who should be prioritised for emicizumab prophylaxis.

In the current South African Health Product Regulatory Authority (SAHPRA)-approved label, emicizumab is indicated for haemophilia A patients with and without inhibitors.[34] The indication includes patients with severe haemophilia A (FVIII level <1%) and those with moderate haemophilia A (FVIII level 1 - 5%) with a severe clinical bleeding phenotype.[35] The expert panel endorsed that patients meeting one or more of the following evidence-based criteria should be considered for initiating emicizumab prophylaxis:

Criteria for patients with haemophilia A with inhibitors

1. Patients with an annual bleeding rate (ABR) >4[8-10,36,37]
2. Patients with a history of (or who are at high risk of) life- or organ-threatening bleeds[1,8,10,27]
3. Patients with an ABR <4 and poor response to bypassing agents[8]
4. Patients with poor venous access[1,8,10,38]
5. Patients with target joints[8,16,10,39]
6. Patients in circumstances where no alternative options are deemed viable by the treating healthcare professional (consensus opinion).

Criteria for patients with haemophilia A without inhibitors

1. Patients with a high bleed rate (ABR >4) despite FVIII prophylaxis[9,40-42]
2. Patients with a history of (or who are at high risk of) life- or organ-threatening bleeds[1,9,43,44]
3. Patients with poor venous access[1,9,38,44,45]
4. Patients with target joints[1,9,16,39,44]
5. Patients in circumstances where no alternative options are deemed viable by the treating healthcare professional (consensus opinion).

Discussion

Treatment for patients with haemophilia has shown a remarkable evolution in the past few decades, with advances in treatment tools and treatment approaches. While prophylaxis was recognised as optimal care for people with haemophilia in 2007, it has not been possible to put it into practice owing to the high cost, high treatment burden and requirement for intravenous access. The new non-factor therapies, such as emicizumab, have enabled the adoption of prophylaxis as the new standard of care in haemophilia. In a resource-constrained setting such as SA, the evidence-based criteria for who should be prioritised for emicizumab will go a long way towards clarifying the role of these novel therapies in optimising haemophilia patient care.

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