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Redefining prophylaxis in the modern era

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Abstract

Prophylaxis is the globally accepted standard of care for persons with haemophilia and presents many advantages over episodic treatment. The prophylaxis benefits include bleed reduction, reduction in musculoskeletal complications and improvement in the quality of life. The currently evolving novel therapies for the management of haemophilia has ushered a new era characterized by improved prophylaxis targets and outcomes. These redefined targets and outcomes have necessitated the need to also redefine prophylaxis. In this state-of-the-art review, we redefine prophylaxis in the modern era by revisiting its definition, presenting data to support higher trough levels to achieve with prophylaxis and introducing steady-state haemostasis as a possible new target for prophylaxis.

KEYWORDS

modern era, novel therapies, prophylaxis, redefinition, steady-state, trough levels

1 | INTRODUCTION

Manco-Johnson et al[1] were the first to prospectively demonstrate in a randomized study the superiority of prophylaxis over episodic treatment in people with haemophilia. Since and even before this landmark study, the many benefits and values of prophylaxis were demonstrated through multiple prospective and retrospective analyses.[2-11] In the modern era, prophylaxis is optimized through several approaches, which include varying the dose, varying the dosing frequencies and exploring alternative routes of administration. The published approaches now include low-dose, intermediate-dose and high-dose prophylaxis regimens depending on the expertise of the treaters, cost of the product and the healthcare system in different countries.

The evolving therapeutic landscape in haemophilia has included registration of several extended half-life products and non-factor haemostatic agents, some of which are now routinely used for prophylaxis.[2,4,12] These therapies have ushered in a new prophylaxis era characterized by less burdensome prophylaxis dosing frequency, and low bleeding rates based, in part, on improved compliance. Some novel therapeutic agents are now administered subcutaneously with consequently improved prophylaxis targets and therapeutic outcomes, especially in patients with inhibitors.[2,4,5,13-15]

It is therefore not surprising that prophylaxis is now the accepted standard of care for all persons with severe haemophilia across geographic and economic sectors of the haemophilia community.[16] In this review, we take a three-pronged approach in redefining prophylaxis in the modern era in the light of all these advances. Dr Victor Blanchete reviews factors defining successful prophylaxis in the changing paradigm of evolving novel therapeutic tools and approaches. Therapies with improved pharmacokinetic properties have enabled us to redefine new targets arising from successful prophylaxis. Dr Robert Klamroth revisits the impact of prophylaxis which aims for higher trough levels. The recent arrival of non-factor haemostatic therapies has allowed us to redefine other prophylaxis endpoints, including targeting steady-state haemostasis as a new potential goal for prophylaxis. Dr Johnny Mahlangu will explore the important role played by steady-state haemostasis in prophylaxis and how prophylaxis was achieved with several non-factor therapies and gene therapy.

2 | DEFINING SUCCESSFUL PROPHYLAXIS: THE PARADIGM IS SHIFTING

The Concise Oxford Dictionary defines prophylaxis as 'preventive treatment against disease' and prophylaxis as 'a medicine or course

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of action tending to prevent disease or other malfunction'.[17] Success is defined as 'a favourable outcome or accomplishment of what was aimed at'.[17] These definitions are important in the context of this review which is aimed at defining successful prophylaxis in the setting of a rapidly evolving therapeutic landscape for persons with severe inherited bleeding disorders. Traditionally, prophylaxis in persons with haemophilia (PWH) was defined as 'the regular replacement of the missing clotting factor given, in anticipation of, and with the intent to, prevent bleeding in persons with haemophilia (PWH)'.[18] This conventional therapeutic protein replacement strategy was pioneered by Professor Inga Marie Nilsson and her colleagues in the Malmo Hemophilia Treatment Centre (HTC) in Sweden in the late 1950s and was adapted by Professor van Creveld and his colleagues in the Netherlands beginning in the 1970s.[19-21] The musculoskeletal (MSK) benefits of long-term prophylaxis started at an early age in young boys with severe haemophilia A or B were striking with the caveat that compliance with the prescribed prophylaxis regimen was critical for a successful long-term outcome, and in some cases, 'failure' of prophylaxis may have been caused by subclinical bleeding not appreciated by the affected individual or caregivers.[1,22] The impressive results of primary prophylaxis reported by the Malmo and van Creveld HTCs were confirmed in the landmark randomized, controlled clinical trial (RCT) reported by Marilyn Manco-Johnson et al[1] and alluded to earlier. The fact that long-term prophylaxis is clearly superior to episodic 'on-demand' therapy is now well-established, and studies have shown that some form of prophylaxis, even low-dose prophylaxis, results in better outcomes than 'on-demand' therapy.[23]

The recent explosion in novel therapeutic approaches for prevention of bleeding in persons with inherited bleeding disorders, in particular both inhibitor negative and inhibitor positive persons with haemophilia A and B, has necessitated a review of the traditional definition of prophylaxis. In a recent review, Carcao et al[24] proposed that prophylaxis be defined as "the regular administration of a haemostatic agent /agents, effectively and conveniently prevent bleeding while allowing PWH to lead active lives". The new, and exciting, prophylaxis therapeutic approaches involve the use of extended half-life products, non-factor replacement therapies as well as gene therapy to prevent bleeds in persons with inherited bleeding disorders.

2.1 | Extended half-life (EHL) clotting factor concentrates (CFCs) for prophylaxis

The predicted extension in the half-life of infused EHL FVIII products is approximately 1.5-fold and that of the EHL FIX products as great as 3-5-fold.[25] The advantage of switching from a standard half-life (SHL) to an EHL FVIII or IX clotting factor concentrate is a clinically significant reduction in the frequency of regular infusions required to achieve the desired trough FVIII/IX level, or a higher trough level while maintaining the same frequency of infusions. Both benefits can be achieved with some EHL FIX CFCs, whereas only one of the two benefits is practically achievable with current commercially available EHL FVIII CFCs.[26] Impressive terminal half-life results with a novel EHL rFVIII concentrate (of the order of 36-41 hours) that circumvents the tight VWF-FVIII association will impact on this limitation once this novel agent achieves regulatory approval.[27]

2.2 | New non-factor haemostatic agents targeted at re-balancing haemostasis

Non-factor haemostatic agents include, but are not limited to: a) the humanized bi-specific monoclonal antibody, emicizumab[2,5]; high-affinity antitissue factor pathway inhibitors (anti-TFPI agents) such as concizumab[28]; and small RNA inhibitors such as Fitusiran that silence the gene for antithrombin and result in decreased levels of this natural anticoagulant.[15] The advantage of these agents over plasma-derived or recombinant haemostatic therapies is that they can be administered subcutaneously with a frequency that varies from once daily to once every four weeks. All of these agents have shown impressive reductions in spontaneous bleeding episodes in patients with haemophilia with or without inhibitors. Emicizumab is now licensed by over eighty regulatory authorities around the world for use in inhibitor negative and inhibitor positive persons with haemophilia A, and the two other novel non-factor haemostatic therapies are in advanced clinical trials.

Gene therapy is the 'holy grail' since it represents the possibility of a life-long phenotypic cure for persons with haemophilia A and B. As haemophilia is still transmissible using the current gene transfer approach, it does not constitute a true cure. Clinical trials in adolescents and adults are very encouraging, and this strategy is sure to assume an increasingly important role in therapeutic options for PWH in the years ahead.[29] Another potentially curative approach, gene editing, is under active investigation for a number of severe inherited haematologic disorders (eg sickle cell anaemia and thalassaemia) and is likely to enter the therapeutic landscape for severe inherited bleeding disorders in the years ahead.[30]

2.3 | Optimal trough factor levels—a shift away from the 1% threshold

The pioneering studies of prophylaxis in Sweden aimed to covert boys with severe haemophilia to a moderate phenotype. In adherent subjects, use of the gold standard 'Malmo' full dose prophylaxis regimen implemented at a very young age and targeted to maintain circulating FVIII/IX trough levels of at least 1% was associated with annualized joint bleeding rates of <1.[20] These observations were confirmed in the USA Joint Outcome RCT.[1] However, very long-term studies (>20 years) of high-dose primary prophylaxis identified that excellent long-term MSK outcomes were not achieved in all cases and that ankles were the index joints most affected by arthropathy.[31] The reason for such 'failures' are multifold

and certainly include poor compliance with the prescribed prophylaxis regimen,[32] variations in pharmacokinetic profiles between PWH following infusion of FVIII/IX,[33] different activity profiles between PWH across the age span of childhood to adulthood and likely because a 1% trough level is simply not adequate to prevent all bleeds in settings of trauma. This realization has led to a shift towards higher target FVIII/IX trough levels. In general, it has been noted that the higher the trough levels the less bleeding persons with haemophilia will sustain up to a level of 10%-12% at which point bleeding virtually never occurs.[34] Of course, for very intense physical activities higher peak FVIII/IX levels are required to protect against spontaneous bleeding.[35]

2.4 | Redefinition of successful prophylaxis

If one accepts success as 'a favourable outcome or accomplishment of what was aimed at' it becomes necessary to define a priori the desired outcome(s) associated with any programme of short-, medium- or long-term prophylaxis. As examples, the goal of life-long prophylaxis introduced from a very early age in persons with severe FXIII deficiency would be to prevent overt and even subclinical spontaneous intra-cranial haemorrhages[36]; for severe VWD (type 3 and some type 2 variants), the goals might be to achieve better control of recurrent severe epistaxis or menorrhagia not controlled by standard medical strategies, or recurrent severe gastrointestinal bleeding in some type 2 VWD variants.[37,38] For PWH at risk for long-term complications of MSK bleeding, the goals would include a clinically significant reduction in spontaneous muscle/joint bleeds and target joint bleeding with preservation of excellent functional MSK status; these goals are now potentially achievable for PWH with and without high-titre inhibitors using EHL FVIII/IX concentrates and/or emicizumab. An interesting sub-group are elderly PWH who may in addition to moderate/severe haemophilia have decreased coordination. Here, the scales may tip in favour of emicizumab prophylaxis for haemophilia A cases because of the decreased burden of administration associated with a subcutaneously versus intravenously (IV) administered haemostatic agent. Finally, there is a growing interest in 'hybrid' prophylaxis regimens where, for example, in very young boys with severe haemophilia A, prophylaxis could be initiated with subcutaneously administered emicizumab in association with low-dose intermittent IV administration of FVIII to identify the subset of boys who will develop high-titre neutralizing inhibitors to FVIII.[37]

3 | DOSING HIGHER TROUGH LEVELS: PROPEL AND OTHER STUDIES

The original idea of prophylaxis was to convert the bleeding pattern of patients with severe haemophilia to that of patients with moderate disease, aiming for a factor trough level above 1%.[1] However, the bleeding phenotype in individual patients is largely variable and not always related to the clotting factor level.[39]

Modern prophylaxis regimens aim for FVIII or FIX trough levels above 1%; such regimens have shown a 90% reduction of the frequency of bleeding in comparison to on-demand treatment.[1,39-41] To achieve the above, often, patients are treated with similar standard prophylaxis regimens. However, given interpatient variability in bleeding phenotype, some persons with haemophilia still may experience bleeds, implying that the same regimen might not be appropriate for all patients, and a personalized approach is needed.[42] Consequently, the focus has switched to adapt the replacement regimen to the individual needs of the individual with haemophilia. For this, much emphasis has been placed on individual subjects FVIII or FIX pharmacokinetic (PK) profiles.[43] Daily low-dose FVIII injections to reduce overall FVIII prophylaxis consumption were attempted, but patients reported a decrease in quality of life, and some of them surprisingly also had an increase in bleeding tendency.[44]

Circulating factor levels are relevant (although not perfect) predictor of bleeding in patients with haemophilia and aiming for a higher trough level to minimize bleeding further is a reasonable approach.[45] Retrospective data imply that the spontaneous ABR is zero when factor levels are above 10%-12%.[46] A recent Delphi consensus by a group of 11 international experts has defined a proposal for different target factor levels for improved prevention of bleeds in patients with haemophilia.[45,47] Depending on age, physical activity, bleeding phenotype and other factors, higher or lower factor levels should be achieved. The choice of a specific target factor level is an important aspect for the implementation of a tailored, personalized regimen for each subject with haemophilia. With the introduction of EHL factor concentrates in clinical care, higher trough levels are easier to achieve, especially in patients with haemophilia B in comparison to SHL factor concentrates.

The PROPEL study was a phase 3, randomized, open-label, multicentre trial evaluating the impact of targeting higher trough levels in severe haemophilia A patients.[48] The study objective was to compare the safety and efficacy of pharmacokinetic-guided prophylaxis with the EHL FVIII rurioctocog alfa pegol (Adynovi/Adynovate) targeting FVIII trough levels of 1%-3% or 8%-12% in subjects with severe haemophilia A. The hypothesis for the comparison was that higher FVIII trough levels increase the proportion of subjects experiencing zero bleeds. Previously treated patients with a FVIII baseline level < 1%, 12-65 years of age and a previous annualized bleeding rate (ABR) ≥2 during the 12 months before study entry were included. Subjects with presence or a history of FVIII inhibitors were excluded.

All patients had a full PK assessment and were randomly assigned to one of the two treatment regimens independent from the results of the PK-study, activity level and bleeding phenotype. The first regimen targeted FVIII trough levels of 1%-3% and the second regimen 8%-12%. The first 6 months served as an observation phase and treatment adjustment period. The evaluation of the primary endpoint (proportion of patients with an ABR of zero) took place in the second 6 months of the study.

A total of 115 subjects were randomized, and 56 completed the study in the FVIII trough 1%-3% arm and 50 in the FVIII trough 8%-12% arm. In the full analysis set, the proportion of subjects in the

FVIII trough 1%-3% arm who had a total ABR of zero was 42%, a spontaneous ABR of zero was 60% and a spontaneous annualized index joint bleed rate (AJBR) of zero was 65%. The proportion of subjects in the FVIII trough 8%-12% arm who had a total ABR of zero was 62%, a spontaneous ABR of zero 76% and a spontaneous AJBR of zero was 85%. With PK-guided dosing, the targeted FVIII trough levels were achieved in both groups. To maintain the desired FVIII trough level, the median number of injections was 2.0 per week in the FVIII trough 1%-3%-arm and 3.6 per week in the FVIII trough 8%-12%-arm. The median prophylactic dose per year was 3454 IU/kg bodyweight in the FVIII trough 1%-3%-arm and more than double that at 7490 IU/kg bodyweight in the FVIII trough 8%-12%-arm. The need for more frequent injections for subjects in the FVIII trough 8%-12% arm resulted in a higher rate of dropouts in this treatment arm in comparison to subjects in the FVIII trough 1%-3%-arm.

No thromboembolic events were observed in the study, and no adverse events led to discontinuation of the study. One patient in the FVIII trough 8%-12% arm tested positive for inhibitors in the Bethesda assay (0.6 BU) at week 8 with no impact on pharmacokinetics, and subsequent inhibitor tests did not confirm this result.

The PROPEL study provided for the first time the proof of concept that patients with severe haemophilia A can benefit from elevated FVIII activity levels because targeting FVIII trough levels of 8%-12% vs 1%-3% resulted in a consistently higher proportion of patients with total ABR, spontaneous ABR and spontaneous AJBR of zero. To reach this goal, more frequent intravenous injections per week and larger consumption of FVIII was necessary. Consequently, adherence and cost are important factors to be considered in PK-guided dosing aiming for higher trough levels. See above.

4 | TARGETING STEADY-STATE HAEMOSTASIS

Clotting factor replacement therapy given proactively (to prevent bleeds) in the management of haemophilia bleeds is characterized by peaks and troughs of plasma factor levels.[49] While factor replacement therapy has been the backbone of haemophilia care for decades, it has several shortcomings which include the high treatment burden and suboptimum compliance,[50,51] difficult to achieve and maintain trough levels exposing patients to frequent breakthrough bleeds and micro bleeds,[1] and the progression of haemophilic arthropathy despite access to treatment.[52] Currently, evolving non-factor therapies, as well as gene therapy, aim to address these challenges of replacement therapy peaks and troughs by targeting steady-state haemostasis.

A steady-state is defined as 'an unchanging condition, system or physical process that remains the same even after transformation or change'.[53] In persons with haemophilia, targeting steady-state haemostasis requires finding a balance between procoagulant and anticoagulant haemostatic activity able to achieve a steady-state despite haemostatic challenges. This would result in patients living a life free of the fear of bleeding, even if they are exposed to haemostatic challenges. While there are many benefits of achieving steady-state haemostasis, there is no consensus on what the steady-state haemostasis target or targets should be. Opinions of some patients, healthcare providers and funders seem to converge towards achieving a steady state in which haemostatic function is normal or near normal. Achieving normal haemostasis in a person with haemophilia requires critical risk-benefit evaluation. Steady-state haemostasis is influenced by multiple factors, which include the type of prohaemostatic agent used, route of administration, dose, dosing frequency, and individual patient pharmacokinetic and pharmacodynamic profiles and as well as targeted therapeutic outcomes.

The value of intravenous administration of prohaemostatic agents aimed at achieving steady-state haemostasis appears to be limited by factors including the agent's intrinsic biological properties (half-life, clearance, etc) and their role in haemostasis. Upon intravenous administration, many prohaemostatic agents have limited intravenous life spans, which impose a high treatment burden when used prophylactically. The possible advantage of intravenous infusion of prohaemostatic agents is in the administration of the loading dose, thereby shortening the time to reach the steady state.[54]

Subcutaneous administration of prohaemostatic agents is currently extensively explored as a way of establishing and maintaining steady-state haemostasis. Many programmes are exploring subcutaneous administration of both clotting factors (factor FVIII and factor FIX) and non-factor therapeutic agents. The non-factor therapies explored in humans include factor VIII mimetic (emicizumab), anti-TFPI (concizumab) and antithrombin(fitusiran) therapy programmes.

Efforts to achieve steady haemostatic state through subcutaneous administration of clotting FVIII have been unsuccessful to date[55] mainly because of the highly immunogenic nature of FVIII when given subcutaneously. Consequently, one programme of subcutaneous administration of FVIII was stopped in the phase 2/3 stage of development.[55] Proof of concept of subcutaneous administration of FIX has now been established in the preclinical models,[56-58] and several studies are currently underway.

Emicizumab has completed three Phase 3 studies in which it is given subcutaneously.[2,4,5] An emicizumab steady-state maintenance plasma level of 45-50 μg/mL was targeted weekly, every two weeks and every four weeks dosing at 1.5, 3 and 6 mg/kg, respectively. All maintenance doses were preceded by a subcutaneous loading dose of 1.5 mg/kg weekly for four weeks. The PK profiles of the various dosing regimens are remarkably similar and consistent across dosing frequency and age. The achieved haemostatic target was associated with very low bleed rates, low clotting factor consumption, resolution of target joints and improvement in the quality of life of subjects receiving emicizumab.

In a Phase 1 RNAi targeting antithrombin programme, steady-state antithrombin reduction was achieved with a once-monthly subcutaneous injection.[15] This approach is currently being explored in an ongoing Phase 2/3 study.

Several TFPI-targeting molecules have been investigated over the years, four of which (concizumab, BAY 1093884, marstacimab and MG1113) are subcutaneous anti-TFPI antibodies that have

entered clinical trials including both haemophilia A and B patients with and without inhibitors. A phase 2 BAY 1093884 trial has now been terminated due to serious adverse events. A Phase 1 concizumab study demonstrated that giving a single injection of anti-TFPI subcutaneously at a dose of up to 9000 μg/kg resulted in a steady-state anti-TFPI level.[14] The steady-state concizumab was not achieved with a single intravenous injection. The Phase 3 programme is currently underway in exploring the subcutaneous injection.

Several Phase 1/2 gene therapy programmes for FVIII and FIX have been reported in the last decade.[59-62] In the multiple-dose programmes, there is a clear dose-dependent target factor level achieved. While gene therapy has the potential for cure, there is an overall wide variability of factor levels achieved post-transgene infusion. This makes targeting steady haemostasis difficult to achieve with the current AAV-based gene therapies. Despite the variability of expression, most subjects do achieve a steady-state factor level, which is protective. All gene therapy participants to date have experienced fewer bleeds, reduction in factor consumption and improved quality of life. Without understanding the reasons for the variable factor expression in gene therapy, targeting steady-state haemophilia in this setting may prove elusive.

Despite the apparent variability in the target haemostatic levels achieved, many studies demonstrate that there are merits in establishing and maintaining steady-state haemostasis. The benefits of targeted steady-state haemostasis include reductions in treatment burden, factor consumption, haemophilia disease burden and improvement in patient quality of life. Compared to replacement therapies, achieving steady-state haemostasis eliminates spontaneous breakthrough bleeds, reduces microbleeds and increases the number of patients achieving zero bleeds.

5 | CONCLUSION

Therapeutic advances in haemophilia care dictate that prophylaxis be redefined to align with modern era evolving therapies. This definition should include what constitutes successful prophylaxis, the impact of higher trough levels on prophylaxis outcomes and setting steady-state haemostasis as a possible target for long-term prophylaxis of persons with moderate/severe haemophilia.

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