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Nonfactor Therapies for Hemophilia

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Hemophilia A and B are X-linked bleeding disorders that have been described in human history for about 2000 years, although it has only been about 200 years since the science of hemophilia has been broadly understood.[1] Once it was identified that patients with hemophilia bleed due to an absence of proteins present in the blood, treatment for bleeding episodes and eventually prophylaxis revolved around replacing those missing proteins (factors VIII [FVIII] and IX [FIX]). The first treatment was a whole blood transfusion in the mid-1800s, but treatments evolved over the next century to using plasma and cryoprecipitate followed by clotting factor concentrates (CFCs), which became widely available in the 1970s. Unfortunately, these original CFCs that were plasma-derived led to an epidemic of AIDS and hepatitis B and C, which resulted in thousands of deaths. This spurred further innovation and in 1992 the recombinant era of CFCs was born, and these products have become the standard of care in well-resourced countries, although plasma-derived CFCs are still used extensively (and they are now essentially free of the risk for infectious diseases) in middle- and low-income countries.

Despite the overall excellent safety and efficacy of these products, they have a number of limitations, which can be separated into issues related to the disease burden and the treatment burden.[2] As for the disease burden, the bleeding rates for those patients receiving prophylaxis remain too high (between 2 and 6 per year in clinical trials) and all but the most recently licensed product (Altuviiio, efanesoctocog alfa, Sanofi, Cambridge, MA)[3] have short enough half-lives such that trough levels between doses hover between 1% and4% typically. It is likely that even in the absence of overt bleeding, subclinical bleeding occurs, which can lead to long-term joint disease. With respect to the treatment burden, all CFCs are administered intravenously, usually multiple times per week, which is challenging for many (young children in particular) and painful and time-consuming for all. This treatment burden at best negatively impacts the quality of life and at worst results in poor adherence, which further worsens the clinical outcomes. As a result of these shortcomings, novel approaches have been sought to both improve efficacy and reduce the treatment burden, which together will improve the quality of life for both patients and their caregivers.

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NONFACTOR THERAPIES

Before embarking on a discussion of these agents, a brief definition is needed. Although there is no formal definition of nonfactor therapies, as the name implies, these are treatments that correct the hemostatic defect without replacing the missing protein (FVIII or FIX). At first glance, it would seem counterintuitive to treat hemophilia without replacing precisely what is missing, and there are people in the hemophilia community including patients who feel more comfortable with CFCs for this exact reason. However, for many other patients, the limitations of the CFCs as described earlier have them yearning for alternatives. So, why approach hemophilia with nonfactor therapies? Obviously, this should be to improve the patient experience, which means less bleeding and a reduced treatment burden. Therefore, nonfactor therapies have all been developed to be given subcutaneously and most of them at less frequent intervals than CFCs (Table 1). In addition, in clinical trials to be discussed below, they also have mostly resulted in reduced frequency of bleeding. If nonfactor therapies do not simply replace the missing protein, then the next question is how do they work? It turns out there are several mechanisms of action that can broadly be classified as factor mimetics and rebalancing agents (Figure 1). Factor mimetics (or substitution therapies) as their name implies function in the same role as factor but without actually being the factor itself, which offers a number of advantages to be discussed below. Rebalancing agents as their name implies improve hemostasis not by increasing factor levels or mimicking that function but rather by reducing or inhibiting the natural inhibitors of coagulation. This allows the limited amount of thrombin generated by hemophilia patients to feedback unto itself and increase thrombin generation resulting in effective clot formation. Lastly, a key property of nonfactor therapies lies in the mere fact that these agents should be able to treat both patients with and without CFC antidrug antibodies (inhibitors). Patients with inhibitors have continued to suffer from worse morbidity and mortality than their counterparts without inhibitors and thus novel therapies were also needed to bridge this major treatment gap.

FACTOR MIMETICS

The first approved nonfactor therapy is the factor mimetic emicizumab (Hemlibra, Roche, Basel Switzerland). Emicizumab is a bispecific monoclonal antibody, which has one arm that binds to FIX/FIXa and the other binds to FX and mimics the cofactor function of FVIII, which enhances the FIXa catalysis

of FX to its activated form FXa.[4] Factor Xa then along with its cofactor, FV, converts prothrombin to thrombin. Emicizumab was developed by the selection from thousands of candidate monoclonal antibodies to have the preferred pharmacologic properties. These include its FIX/FIXa and FX binding properties as well its ability to function when administered subcutaneously and its half-life, which at ~30 days allows for dosing to be weekly, biweekly or every 4 weeks. Emicizumab has been and continues to be extensively studied in the HAVEN series of studies. The pivotal trials (HAVEN 1–4) have been extensively discussed in other publications and the details of each study are beyond the scope of this brief review.[5–8] Suffice it to say that the trials demonstrated efficacy and safety in hemophilia A patients of all ages and for those with and without inhibitors. Not surprisingly, given the reduced bleeding rate and, perhaps even more valued by patients and caregivers, the significantly reduced treatment burden, emicizumab has in many countries supplanted FVIII CFCs as the most prescribed medication for prophylaxis. Additional studies in different patient populations than originally studied such as infants in the HAVEN 7 study in addition to studies in other indications such as acquired hemophilia and von Willebrand disease are ongoing.

Although emicizumab has undoubtedly revolutionized the care for hemophilia patients, especially those with inhibitors, there is, nevertheless, room for improvement. It has been demonstrated through a variety of approaches that emicizumab converts patients to a mild hemophilia phenotype, and improved outcomes, particularly for active patients, are needed. Building upon the same mechanism of action, there are several candidate "next generation" factor VIII mimetics. One of these, Mim8 (Novo Nordisk, Bagsvaerd, Denmark) is currently in phase 3 clinical trials and has been shown in vitro to be at least one log more potent than emicizumab.[9] Whether this will result in improved outcomes without compromising safety remains to be seen.

Table 1

Novel Medications for Hemophilia by Infusions Per Year

Drug	Infusions Per Year	Comments
Factor replacement	52–183	Only intravenous Other administration methods have been tried but have not been found to be safe
Emicizumab/Mim8	13–52	Very long washout (months) with no antidote
Fitusiran	6–12	Very long washout (months) but with an antidote (antithrombin infusion)
Concizumab	365	Daily infusion, but advantage of rapid washout No antidote
Marstacimab	52	No antidote
Serpin PC	13–52	Dosing still being worked out

REBALANCING AGENTS

When functioning properly, the hemostatic system, composed of prohemostatic proteins and their inhibitors, works to ensure that people are subject neither to excessive bleeding nor excessive clotting (Figure 1). Reduced amounts of prohemostatic proteins such as FVIII or FIX result in excessive bleeding (hemophilia), whereas reduced amounts of coagulation inhibitors results in excessive clotting (thrombophilia). As mentioned earlier, the classic treatment for hemophilia is to restore the balance of hemostasis by adding back FVIII or FIX in the form of CFCs or with novel approaches such as emicizumab. An alternative rebalancing approach could be to reduce the quantity or function of the coagulation inhibitors antithrombin, tissue factor pathway inhibitor (TFPI), protein C or protein S. There are extremely rare patients who coinherited hemophilia along with a deficiency of one of the above coagulation inhibitors and they

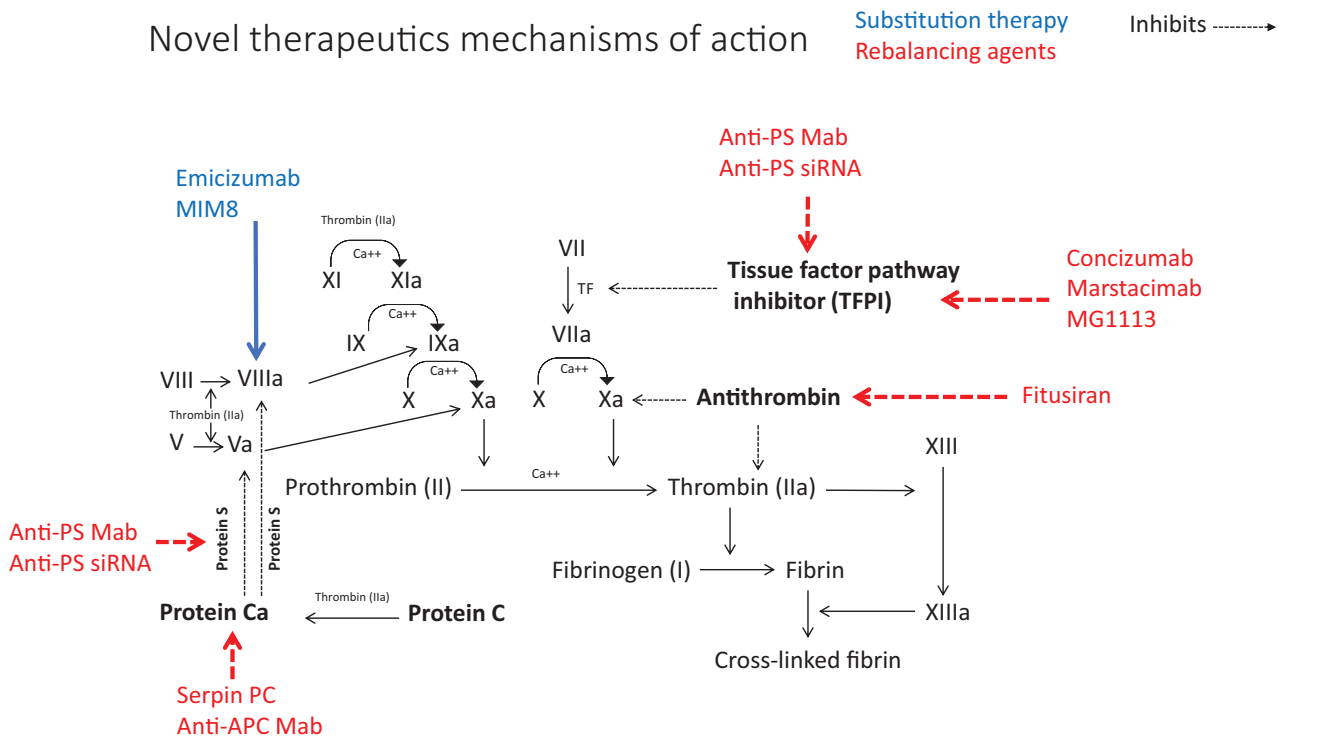

Figure 1. Novel hemophilia therapies presented by their mechanism of action in the coagulation cascade.

seem to have neither excessive bleeding nor excessive clotting—they are naturally rebalanced per se.[10]

Although several of these agents are in phase 3 clinical trials, none are as yet approved. These agents can be further divided according to the coagulation inhibitor they aim to suppress. Fitusiran reduces the amount of antithrombin in the circulation, while concizumab, marstacimab, and MG1113 reduce the circulating pool of TFPI. Serpin PC depletes the pool of activated protein C (APC), while several candidate molecules reduce the pool of protein S, which is the cofactor for APC. These agents are all administered subcutaneously and are planned to be given daily, weekly, monthly, or every other month (Table 1). A key difference between rebalancing agents and factor mimetics is the broader patient population that can benefit from these agents. Because these drugs do not specifically target any 1 protein as emicizumab and Mim8 substituting for FVIII, they can be used in patients with both hemophilia A and B and as aforementioned those with and without inhibitors. Another important aspect of rebalancing therapies revolves around safety. Can one get the balance right? That is, correct hemostasis and reduce bleeding, but not overcorrect and result in a significant risk for thrombosis. Data emerging from the clinical trials suggests that thrombosis is indeed a risk when using these agents; however, for most of the products, the benefit to risk ratio has favored continued development. Notably, one anti-TFPI molecule, befovacimab (Bayer, Whippany, NJ) led to enough of a thrombosis concern that its development was discontinued.[11]

Reviewing all the clinical trial data for these agents is beyond the scope of this review; however, a few key points will be made below. First, the only drug for which phase 3 clinical trial data is fully published is fitusiran in the recent publications of the ATLAS-INH (inhibitor patients) and ATLAS A/B (noninhibitor patients) trials.[12,13] Both trials compared once monthly 80 mg subcutaneous doses of fitusiran to on-demand treatment with bypassing agents (ATLAS-INH) or CFCs (ATLAS A/B) and clearly demonstrated the superiority of fitusiran over on-demand treatment. Although one could argue that for noninhibitor patients, this is not currently a fair comparison, for inhibitor patients, it is important to note that the ATLAS-INH study was initiated before emicizumab was widely available and furthermore, there is no currently effective mode of prophylaxis for hemophilia B patients with inhibitors. Nonetheless, these trials confirm the efficacy of fitusiran as a prophylaxis agent for hemophilia A and B patients with and without inhibitors. The ATLAS-PPX study compares fitusiran with prophylaxis with bypassing agents (inhibitor patients) and CFCs (noninhibitor patients), and early data presented in abstract form have demonstrated that fitusiran is indeed more effective than either of those options.[14] As for safety, thrombotic events have been reported with fitusiran, although the overall rate from the phase 3 studies has been <5% and the benefit in the view of this author outweighs this risk. Other adverse events included increased alanine aminotransferase levels, which while in general not >3 times the upper limit of normal and not leading to study drug discontinuation continues to be monitored in the ongoing trials. Lastly, cholelithiasis seems to also be an emerging concern with this agent, although again the benefits outweigh the risks. The etiology of these off-target adverse events is being investigated in the phase 3 trials.

With respect to the anti-TFPI agents (concizumab and marstacimab), the published phase 2 and phase 1 of 2 trials, respectively, have demonstrated reasonable efficacy thus far. Phase 3 clinical trials are under way for all categories of hemophilia patients as mentioned earlier. Although both of these agents are monoclonal antibodies, concizumab is given subcutaneously once daily, whereas marstacimab is administered once weekly.[15,16] While this would generally be seen as a disadvantage for concizumab, the use of a specialized pen device with refillable cartridges may make this process simple enough that the frequency of administration may not, in fact, be as burdensome as it seems. Furthermore, its relatively short duration of action may be a favorable quality in patients with comorbidities or those who may need surgical procedures as it would only take a few days to wash out as opposed to the longer duration of action of marstacimab and the other nonfactor therapies described earlier.

Finally, agents inhibiting the protein C and S system are also in clinical development with serpin PC, a leading candidate among these agents. Promising results have been shown in the phase 1 study and phase 3 studies are under way.[17]

In conclusion, nonfactor therapies have already started to have a significant role in the treatment of hemophilia (emicizumab) and will likely have even more impact as other nonfactor therapies with a variety of mechanisms of action become widely available.

AUTHOR CONTRIBUTIONS

GY conceived and wrote the article.

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