Therapy for haemophilia: recent advances and goals for the future

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In the 20th century, haemophilia evolved from a life-threatening, crippling disease to one for which the prognosis is excellent and many patients lead normal, productive lives. Although dramatic achievements in the treatment of haemophilia have occurred, the current therapies have significant drawbacks. Among these is the relatively high incidence of inhibitor development, the requirement for frequent intravenous infusions to prevent bleeding complications, the lack of effective treatment for established joint disease, and the high cost of treatment. The future goal of haemophilia treatment first and foremost is curing this genetic condition via gene therapy. As this goal is likely many years away, improvements in the current factor products in order to reduce the development of inhibitors and to reduce the frequency of therapy are more immediately achievable goals. Finally, improving the treatment of bleeding complications, particularly in inhibitor patients, and developing novel adjunctive therapies for the management of joint disease are also important goals for the near future. This review will discuss in detail the current and future goals of haemophilia therapy.

Keywords: haemophilia, inhibitors, therapy


1. Background

The haemophilias are a group of related bleeding disorders caused by a deficiency of specific coagulation proteins called factors [1]. The most common deficiencies are those of Factors (F) VIII, IX and XI [2]. Other factor deficiencies are much less common (von Willebrand disease is the most common bleeding disorder, but will not be discussed in this review, which will focus on haemophilia). Because FXI deficiency leads to relatively few symptoms, the vast majority of patients with clinically significant haemophilia have deficiencies of Factors VIII and IX. These disorders are classified as mild, moderate or severe and can lead to significant pathology, mostly involving the joints. As such, major advances in the treatment of haemophilia revolve around correction of these deficiencies with factor concentrates as well as management of the complications of joint disease known as haemophilic arthropathy [3].

2. Existing treatment

Haemophilia was first recognised in the Talmud about 1800 years ago [4]. However, it was not until the mid-19th century that it became recognised that transfusion therapy could treat bleeding in such patients, and not until the middle of the 20th century when the clotting factors were discovered that led to the use of fractions of whole blood for treatment. The development of factor concentrates and comprehensive haemophilia treatment centres, as well as the initiation of treatment in the home, significantly improved the lives of patients with haemophilia who previously were often crippled by recurrent joint bleeding. This led to an era of dramatic improvement in survival and quality of life for patients with these previously devastating disorders [5].
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Table 1. Currently available Factor VIII and IX concentrates.

<table>
<thead>
<tr>
<th>Factor VIII concentrates</th>
<th>Advantages</th>
<th>Disadvantages</th>
<th>Comments</th>
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<tbody>
<tr>
<td>Recombinate™ (Baxter)</td>
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<tr>
<td>Kogenate® FS (Bayer)</td>
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<td>Helixate® FS (ZLB Behring)</td>
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<td>RefFacto® (Wyeth)</td>
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<td>Advate (Baxter)</td>
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<td>Monoclate P® (ZLB Behring)</td>
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<td>Hemophil-M (Baxter)</td>
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<td>Monarc™ (American Red Cross)</td>
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<table>
<thead>
<tr>
<th>Factor IX concentrates</th>
<th>Advantages</th>
<th>Disadvantages</th>
<th>Comments</th>
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<tbody>
<tr>
<td>Benefix (Wyeth)</td>
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<td>Mononine® (ZLB Behring)</td>
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<td>Proplex® T (Baxter)</td>
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<td>Profilnine® (Grifols)</td>
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<td>Konyne® 80 (Bayer)</td>
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Note: Both Humate P (ZLB Behring) and Alphanate (Grifols) are commercially available Factor VIII products. However, their use currently is limited to patients with von Willebrand disease (only Humate P is licensed for use in von Willebrand disease).

Unfortunately, the emergence of human immunodeficiency virus (HIV) as a contaminant of the world blood (and factor) supply led to the majority of severely affected patients contracting HIV and subsequently acquired immune deficiency syndrome (AIDS) [6]. This led to many patients shunning factor concentrates for legitimate concerns of contracting AIDS, which set back the significant achievements of patients with haemophilia for many years. The devastating effects on the haemophilia community spurred efforts into developing safer products including ones not derived from human plasma. These efforts resulted in extraordinarily rapid developments, from the development of viral inactivation methods (heat treatment, solvent-detergent treatment, and recently nanofiltration, which have essentially eliminated the threat of HIV, hepatitis B virus [HBV] and hepatitis C virus [HCV]) for plasma-derived products still in use today to the cloning of the genes for FVIII and FIX and the eventual development of recombinant factor concentrates, which are in use in most patients today in the industrialised world (Table 1) [7]. Although recombinant products are preferred (MASAC #106) [101], it is recognised that most of patients worldwide do not have access to these products due to economic constraints, and that virally-inactivated plasma-derived products have not been demonstrated to transmit HIV, HBV and HCV, and are considered to be very safe from the standpoint of infectious disease transmission. The threat of emerging pathogens such as West Nile virus and prions to virally inactivated products, however, remains to be determined [8].

Currently, therapy for severe haemophilia often incorporates prophylactic infusions of factor concentrates (especially in children), which leads to the prevention of joint disease and allows for a near normal lifestyle. The Swedish cohort, which has received continuous prophylaxis from an early age for >30 years, has demonstrated that prophylaxis can completely prevent not only joint disease but other bleeding complications, thus allowing patients to lead high quality productive lives [9,10].
3. Medical need

Although widespread availability of safe replacement factor products and prophylaxis has dramatically improved the outcome for haemophilia patients, there are several disadvantages to current therapy (see Table 2). First, there are several aspects of prophylactic therapy which lead to its underutilisation despite its effectiveness [11]. Factor concentrates are only effective if administered intravenously. This, combined with the relatively short half-life of both FVIII and FIX, leads to the requirement for frequent (2 – 3 times weekly) intravenous infusions, which many patients and their families find inconvenient. In younger children, the feasibility of such regular infusions often leads to the need for central venous access devices (CVAD), which have potential complications of their own including infection and thrombosis [12]. The development of inhibitors is the most serious complication associated with the use of factor concentrates. Although most inhibitors are either transient or resolve with immune tolerance therapy, ~15% of FVIII-deficient patients and 3% of FIX-deficient patients have persistent clinically significant inhibitors, which result in severe morbidity [13,14]. Finally, although the risk of transmission of infectious agents has been largely overcome by the development of recombinant factor products, there still exists at least the theoretical risk of infection from prions and unforeseen infectious agents perhaps from the use of mammalian cells in the production of factor concentrates [15]. Future treatment for haemophilia revolves around improving on these negative aspects of therapy. This review will discuss recent advances in the management of haemophilia patients as well as potential future therapies such as gene therapy, bioengineered factor replacement products, novel production techniques, and new approaches in the management of inhibitor patients. Additional (non-factor) therapeutic approaches to the management of bleeding and its complications will also be discussed.

4. Therapeutic class review

Over the past decade, a number of recombinant factor concentrates have been introduced that have largely replaced the use of plasma-derived factor (see Table 1 for currently available factor concentrates). For FVIII, they are divided into three
groups or generations [7]. The first-generation products contain albumin derived from human plasma in the final product. The second-generation products contain albumin in the manufacturing process, but it is removed in the final step of purification. The latest product contains no albumin in either the processing or the final product. Most of the factor concentrates are full-length human Factor VIII. However, one product does not contain the B-domain and is thus known as B-domain-deleted FVIII (BDD-FVIII). The BDD-FVIII appears to be as effective as the other products in clinical trials. However, some recent data suggests more breakthrough bleeding in patients using this product, which is more than likely due to inaccuracies in assaying the amount of FVIII per vial and the increased difficulty of measuring plasma FVIII activity rather than due to the inferiority of the product [16]. Although no recombinant FVIII product has ever been known to transmit an infectious disease, some in vitro studies have demonstrated the presence of transfusion-transmitted virus in some lots of first-generation products [17]; although a follow-up study (from the manufacturer of the product in question) [18] disputed this initial report. No additional reports indicating contamination of recombinant products have been published. Currently, the only available first-generation product is likely to be phased out of production as the newer albumin-free formulations are used more extensively. With each new product, significant debate arises regarding whether the additional theoretical safety of the new product is worth the added cost [19].

The currently available factor concentrates are generally very effective and safe, but require frequent administration if prophylaxis is to be used. One novel approach is to administer factor less frequently (once a week, for example). This improves on the issue of inconvenience and more importantly reduces the need for CVAD. Although this approach has been successful in some patients [20], further study is needed in a large number of patients over a long period of time to ensure that such therapy is as effective at preventing joint disease as traditional prophylaxis before such therapy can be recommended for all patients. In addition, the physiology of once-weekly treatment needs explanation. Considering the relatively short half-life of both recombinant FVIII and FIX, once-weekly therapy leaves a sizable period of time when there is no measurable level of circulating factor.

5. Current research goals and potential development issues

The ultimate goal of haemophilia treatment is to cure the disease via gene therapy. However, this elusive goal is likely many years away. In the more immediate future, bioengineering of factor concentrates will lead to products with improved biological properties. An additional goal is to improve the treatment for patients with inhibitors, including reducing the incidence of inhibitor development, improving eradication of inhibitors once they develop, and improving the effectiveness of haemostatic agents. One additional goal is to develop novel adjunctive approaches for the management of joint disease. All of these points will be discussed below (see Table 2).

5.1 Gene therapy

Haemophilia is felt to be one of the best candidates for a disease that can be cured with gene therapy [21,22]. Some of the reasons for this optimism include the fact that therapeutic efficacy is easy to measure both clinically and with laboratory assays of factor levels, that modest increases in the circulating levels of these proteins can lead to significant improvements in symptoms, that the therapeutic window is large, and that gene expression can occur in a variety of tissues with resultant increases in circulating protein levels. So far, several small clinical trials have demonstrated temporary and very small increases in factor levels in a few patients with FVIII and FIX deficiency with relatively little toxicity [23-26]. Furthermore, there have been rapid advances in the field, especially in improving the quality of vectors and improved gene transfer technology. This optimism is tempered by the fact that gene therapy for haemophilia and other diseases is hazardous as the knowledge of potential short- and long-term adverse effects remain unknown. These hazards include death (from an overwhelming immune response directed against the vector) [27], malignancy (occurring several years after gene transfer in two immunodeficiency patients) [28], and germ-line mutations [29]. Thus, although significant scientific progress has been made in the field of gene therapy for haemophilia, it is likely to be many years (at least 10 in the authors’ opinion) before this technology will be made effective and safe for widespread use.

5.2 Bioengineering of improved factor molecules

As mentioned, the major drawbacks to current factor products are the development of inhibitors and the relatively short half-life. Factor XIII, for example, has a long half-life allowing for monthly replacement therapy to achieve adequate prophylaxis [30]. Bioengineering of FVIII and FIX by several groups with the aim of producing a molecule with improved biological properties and reduced immunogenicity has shown promise in preclinical studies. The University of Michigan team led by Randal Kaufman and Steven Pipe has explored the effects of modifying the amino acid sequence of FVIII in order to improve expression and secretion in mammalian cells, increase FVIII activity, and prolong FVIII half-life [31,32], whereas Peter Lollar at Emory University has pioneered methods at reducing FVIII immunogenicity [33]. Advances in the bioengineering of FIX have not been as dramatic as for those of FVIII, and are further away from clinical trials. Nevertheless, modifications of the molecule have been demonstrated to improve production [34,35] and activity [36]. Improvements in expression and secretion in mammalian cells may allow for significantly higher yields of product in the manufacturing process, potentially reducing the cost of production and ultimately the cost of factor. Of more importance, however, is the potential improvement in
physiological function of FVIII. A rFVIII concentrate with improved activity may allow for better clot formation, thereby reducing the need for additional doses to treat a bleed. Another strategy to increase the activity of FVIII is to develop a molecule whose activated form (FVIIIa) is more resistant to proteolysis by activated protein C or a molecule in which dissociation of the A2 domain is prevented. This would allow for increased thrombin generation from the same dose of infused factor, again resulting in improved haemostasis. Another approach to improving the physiological function of FVIII is to increase its half-life [37,38]. Such a molecule could have significant implications for prophylaxis by improving compliance and reducing complications associated with CVAD, thereby leading to less chronic disease. Finally, reducing antigenicity could help prevent inhibitor development, the most serious complication of factor therapy. One concern for an improved FVIII is the development of thrombotic complications, as elevated FVIII is now a recognised risk factor for the development of thrombosis [39]. Although clinical trials with such products have not begun as yet, the promising results in preclinical studies will likely lead to clinical trials in the future. Besides the development of factor products with improved pharmacokinetic properties, bioengineered FVIII and FIX molecules may be used in gene therapy to facilitate achievement of therapeutic levels of non-immunogenic factor [40].

5.3 Novel production techniques

A major shortcoming of standard haemophilia therapy is the extremely high cost of production of factor concentrates. This creates significant pharmacoeconomic issues in industrialised nations and essentially denies optimal therapy to patients in developing nations. It is critically important to develop novel methods to reduce the cost of production and thus the cost of concentrates. The first attempt to improve production methods was to remove the B-domain from the recombinant gene. This led to increased efficiency of translation and improved the yield of production of FVIII from mammalian cells [41]. This product (recombinant B-domain deleted Factor-VIII [rBDD-FVIII], ReFacto®, Wyeth, Andover, MA) is commercially available. However, the small reduction in overall cost of production of a unit of factor has not led to a significant reduction in the cost of the final product, which is similar to that of other recombinant products. Bioengineering of FVIII and FIX as discussed above has the potential to further improve production techniques and perhaps reduce the cost of production. However, it is probable that market forces for such novel techniques will not allow for a significant reduction in the cost of the final product. More recently, production of factor in transgenic farm animals with expression of large amounts of factor in animal milk has been achieved [42,43]. It is hoped that this technique once refined will ultimately lead to production of large amounts of factor inexpensively and perhaps lead to the affordability of recombinant factor products in the developing world.

5.4 Treatment of inhibitor patients

A major goal for the management of haemophilia is to reduce the incidence of inhibitor development. So far, all of the new recombinant FVIII products have demonstrated a similar incidence of inhibitor formation of around 30% [13]. Although some of these inhibitors are transient, many patients require expensive and inconvenient immune tolerance therapy, which, although successful in ~70% of patients, requires large amounts of frequently administered factor for many months and occasionally years [44]. Some experimental approaches at preventing inhibitor formation include bioengineering of factor as discussed above, delaying the use of factor concentrates [45], administering factor concentrates with immune suppressing medication [46,47], and even early introduction of factor concentrates [48]. A few small studies have demonstrated that inhibitor development is more common in patients who receive large amounts of factor concentrates early in life [49]. If such data are confirmed in additional studies, delaying the use of factor concentrates may be one way to prevent inhibitors, and could be considered in patients at especially high risk, such as those with mutations that predispose to inhibitors, and those with a family history of inhibitors, for example. This would need to be balanced with the potential benefits of early prophylaxis. Although some experiments in mice whereby factor concentrates were administered concomitantly with anti-CD40 ligand [46] or anti-CTLA4 [47] (to block the B7-CD28 pathway) nearly eliminated inhibitor development, studies in humans did not demonstrate a prolonged benefit [50]. Additional studies in animals have demonstrated that induction of tolerance via factor infusions on day of life zero is effective at preventing inhibitor formation [48]. Although the above data are intriguing, further studies are needed to determine the best methods to prevent inhibitor formation, and this should remain a focus in haemophilia research until substantial reductions in inhibitor formation are achieved.

A second goal of current research in inhibitor patients is to improve the outcome and reduce the cost and inconvenience of immune tolerance therapy. At this time, there are several therapeutic regimens for immune tolerance induction ranging from low doses of factor given every other day to much larger doses given daily and regimens that incorporate immunosuppressive therapy along with factor infusions (Malmo regimen) [44]. Most of this data and the subsequent discussion below is limited to FVIII deficiency. Inhibitors to FIX are less common and there is a paucity of data from which to make recommendations for the management of FIX inhibitors. Unfortunately, these trials lacked uniform criteria for patient eligibility and were not controlled, thus leading to a lack of consensus on the best approach. A recent systematic review suggests that the Bonn protocol may be more effective than the Malmo protocol or the low-dose protocol [51]. Currently, the International Immune Tolerance Study under the direction of Donna DiMichele and Charles Hay is actively recruiting patients from many countries. This study is randomising patients to 50 units/kg every other
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Table 3. Currently available concentrates for inhibitor patients.

<table>
<thead>
<tr>
<th>Factor concentrate</th>
<th>Advantages</th>
<th>Disadvantages</th>
<th>Comments</th>
</tr>
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<tbody>
<tr>
<td>PCCs</td>
<td>Relatively inexpensive</td>
<td>Not as effective as APCCs</td>
<td>APCCs have largely supplanted the use of PCCs in inhibitor patients</td>
</tr>
<tr>
<td>APCCs (FEIBA)</td>
<td>Long history of use</td>
<td>Potentially thrombogenic (mostly demonstrated in older publications)</td>
<td>Recent data suggest the risk of thrombotic complications with standard doses is low</td>
</tr>
<tr>
<td></td>
<td>Long half-life relative to rFVIIa</td>
<td>No measurable laboratory parameter</td>
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<tr>
<td>rFVIIa</td>
<td>Recombinant product with no requirement for human plasma proteins in production</td>
<td>Short half-life leading to the need for multiple daily doses</td>
<td>Two current clinical trials are assessing rFVIIa versus FEIBA and one is assessing two dosing regimens for rFVIIa</td>
</tr>
<tr>
<td></td>
<td>Efficacy of ~ 90% with about two doses in clinical trials</td>
<td>Efficacy in clinical trials does not seem to translate to clinical practice</td>
<td>A few reports describe thromboelastography and thrombin generation assays as an effective laboratory parameter</td>
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<tr>
<td></td>
<td>Low rate of thrombotic complications</td>
<td>Most effective dosing regimen is unknown</td>
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APCC: Activated prothrombin complex concentrate; FEIBA: Factor eight inhibitor bypass activity; PCC: Prothrombin complex concentrate.

day to 100 units/kg daily. Hopefully, this study will determine the most efficacious and cost effective approach for the eradication of inhibitors. Although immune tolerance therapy as described is the only established treatment for the eradication of inhibitors, other approaches are being considered. There are several reports describing the achievement of tolerance utilising a FVIII product that contains von Willebrand factor in patients who had previously failed to achieve tolerance with pure FVIII concentrates [52]. The mechanism for this response is unknown but undoubtedly involves von Willebrand factor in some way. Further studies are indicated in not only patients in whom immune tolerance failed with recombinant FVIII, but also as a first-line approach. Alternatively, a recent report of two cases (one FVIII and one FIX deficiency) demonstrated the use of the anti-CD20 antibody rituximab for the eradication of haemophilia inhibitors in patients that did not respond to conventional immune tolerance therapy. The patient with the FVIII inhibitor had resolution of the inhibitor with a follow-up of 11 months. However, the therapy failed for a patient with a FIX inhibitor [53]. Such therapy is effective in a number of autoimmune diseases; however, the nature of the antibodies in inhibitor patients is different as these are ‘naturally’ occurring alloantibodies arising from an appropriate immune response to a ‘foreign’ protein, as opposed to a loss of tolerance to self antigens as is the case in autoimmune disease. Although this approach is intriguing, controlled studies will need to be performed in order to deem such therapy appropriate, especially as a first-line treatment. In addition to the above approaches, which are currently available, there are some novel experimental approaches that may offer improvements in the future. One such approach is to selectively suppress CD4+ T cells that are specific for FVIII epitopes [54]. Another entirely different approach is aimed at reducing the neutralising effect of the inhibitory antibody rather than eradicating it by using peptide decoys that mimic the binding site of the epitope on FVIII [55]. In theory this approach may allow inhibitor patients to be treated with replacement FVIII as in non-inhibitor patients.

Another important goal for inhibitor patients is to improve the management of bleeding symptoms and to prevent chronic joint disease. The management of bleeding episodes in inhibitor patients depends on the patient’s inhibitor titre as well as whether the inhibitor is a low- or high-responding inhibitor. Other important factors to consider when selecting the best haemostatic therapy for each bleed in a given patient include the severity and location of the bleed as well the availability of specific therapies and the patient’s previous response to specific therapies. For example, a low titre, low responder patient with a simple haemarthrosis can be treated with standard factor replacement albeit at higher doses. For patients with high titre inhibitors, however, standard factor replacement is generally not effective. At present, there are only two haemostatic agents available for the management of bleeding in patients with high titre inhibitors (Table 3). These are activated prothrombin complex concentrates ([APCC], Factor Eight Inhibitor Bypass Activity [FEIBA], Baxter, Glendale, CA) and recombinant Factor VIIa ([rFVIIa], NovoSeven, Bagsvaerd, Denmark). Previously, porcine Factor VIII was another option. However, it is currently no longer available, and although prothrombin complex concentrates are still available, they have been supplanted by APCC for the management of bleeding in inhibitor patients. Although both APCC and rFVIIa demonstrate excellent efficacy in clinical trials (around 90%) [56,57], the actual clinical efficacy is less than that reported in clinical trials in the opinion of many treaters. Furthermore, some patients do not respond well to either therapy and develop significant bleeding complications.
and chronic joint disease. There are currently two clinical trials aimed at establishing the efficacy of the two agents in comparative trials. In addition, one of these trials is also testing the hypothesis that a single higher dose (270 µg/kg) of rFVIIa is more effective than the currently approved dosing (90 µg/kg for three doses) with a placebo-controlled double-blind method. The results of these studies should be available in the next year. Data from uncontrolled trials suggest that higher doses of rFVIIa (200 – 300 µg/kg/dose) are more effective than the currently approved dose range (90 – 120 µg/kg/dose) [58-60].

Another recently published approach for bleeds that are refractory to either agent alone is to use sequential therapy with both FEIBA and rFVIIa. One study demonstrated improvement in the activated clotting time in inhibitor patients treated with FEIBA for whom rFVIIa was added ex vivo [61]. Furthermore, a report on the use of sequential therapy with APCC and rFVIIa demonstrated the safety of this approach and suggested efficacy in 91 patient-days of therapy with no patient demonstrating clinical or laboratory evidence of thrombosis or disseminated intravascular coagulopathy [62]. Besides therapy aimed at treating bleeding episodes once they occur, there are several small reports that describe the use of APCC or rFVIIa for prophylaxis of bleeding in inhibitor patients. Such therapy has been advocated for particularly difficult patients who develop either multiple, significant bleeding episodes or target joints. Data for the prophylactic use of FEIBA from a small uncontrolled trial demonstrated improvement in arthropathy in two of seven patients, thus leading to their ability to return to school [63]. There are two reports describing the use of rFVIIa given in a prophylactic mode. Combined, the two reports describe the treatment of three patients (two with target joints and one with multiple severe bleeding episodes) with resolution of the target joints and reduction in severe bleeding episodes and reduced hospitalisations [64,65]. A clinical trial evaluating the safety and efficacy of rFVIIa given once daily at a dose of either 90 or 270 µg/kg (in a blinded fashion) is underway. A clinical trial of prophylaxis with FEIBA is also underway. Although there is no doubt about the efficacy of prophylactic factor replacement in non-inhibitor patients, there are as yet no firm data supporting the use of prophylaxis in inhibitor patients. It is the authors’ opinion that prophylaxis for inhibitor patients with either APCC or rFVIIa should only be considered for the most severely affected patients such as those with recurrent life- or limb-threatening bleeds or those for whom target joints develop for whom other approaches such as synovectomy are not feasible.

Despite the reasonable efficacy of FEIBA and rFVIIa, novel haemostatic therapies for inhibitor patients with improved efficacy and safety are warranted. One approach involves the bioengineering of rFVIIa to improve its biological profile by enhancing thrombin generation [66]. Another group has demonstrated both in vitro and in vivo (in a monkey model) that combining plasma-derived FVIIa with plasma-derived FX resulted a longer duration of thrombin generation as compared with rFVIIa alone, but without the thrombogenicity of APCC [67]. Preclinical studies are ongoing in the development of these agents. Another approach is to improve the safety and availability of porcine Factor VIII by developing recombinant porcine Factor VIII [68]. A clinical trial of this agent, termed OBI-1, is underway. See Table 4 for current and future developments in inhibitor patients.

**Table 4. Current and future improvements for inhibitor patients (see Table 3 for methods to prevent inhibitor formation).**

<table>
<thead>
<tr>
<th>Shortcoming</th>
<th>Technique</th>
<th>Current availability</th>
<th>Comments/future availability</th>
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<tbody>
<tr>
<td>Ineffective (less effective than standard factor) haemostasis with currently available agents</td>
<td>Use agents (APCC and rFVIIa) in combination</td>
<td>Yes</td>
<td>Small case series demonstrated safety and suggested efficacy</td>
</tr>
<tr>
<td>Few available effective agents</td>
<td>Develop new agents</td>
<td>No</td>
<td>Recombinant porcine FVIIa (OBI-1) in clinical trials (potentially available in next few years)</td>
</tr>
<tr>
<td>Current agents with short half-life (rFVIIa) or plasma-derived with history of thrombogenicity (APCC)</td>
<td>Bioengineer rFVIIa to have a longer half-life</td>
<td>No</td>
<td>Novel superactive rFVIIa molecules are in preclinical testing Early evidence of the synergistic effect of rFVIIa and FX</td>
</tr>
<tr>
<td>Inability to prevent bleeding episodes</td>
<td>Use rFVIIa or APCC prophylactically</td>
<td>Yes</td>
<td>Limited evidence demonstrating efficacy in a few patients Clinical trial of prophylactic rFVIIa and FEIBA are under way</td>
</tr>
<tr>
<td>Inability to eradicate inhibitors in all patients</td>
<td>Improve immune tolerance therapy with factor Use novel currently available agents</td>
<td>Yes</td>
<td>International clinical trial underway Case report of resolution with rituximab</td>
</tr>
</tbody>
</table>

APCC: Activated prothrombin complex concentrate.
Nevertheless it felt that other COX-2 inhibitors should be further investigated and still be considered for use in haemophilia patients with joint disease, as this patient population is somewhat protected from cardiovascular disease [71,72], and is generally younger than the patients on the rofecoxib clinical trials. Furthermore, improvement in joint function and reduced pain should lead to increased physical activity, which should mitigate the increased cardiovascular risk caused by these medications. Only through randomised, placebo-controlled trials will the efficacy and safety of COX-2 inhibitors be realised for this patient population.

Another class of agents that may be of use in managing synovitis are the anti-TNF-α inhibitors (remicade and etanercept). Both agents are effective in the management of rheumatoid arthritis, a condition with similarities to chronic haemophilic arthropathy. So far, there are no reports assessing these agents in haemophilia patients; thus, the authors cannot support the use of these agents in haemophilia. Clinical trials are warranted.

Another mode of therapy, which although not novel, has been used more extensively for haemophilia patients in recent years is radioisotopic synovectomy [73]. This procedure entails the injection of a radioisotope (usually $^{32}$P) into the affected joint with the goal of destroying the hypertrophied synovial tissue and preventing its reaccumulation. This treatment is currently indicated for patients with target joints who do not respond to factor prophylaxis, and is in lieu of more invasive arthroscopic and open surgical synovectomies. This treatment approach has had an overall high rate of success with minimal complications. A concern with this approach as with all radiation therapy is the potential for development of malignancy. Recently, two cases of leukaemia have been noted in children who underwent radioisotopic synovectomy, further raising concerns about the safety of this approach (personal communication). The authors recommend that for patients who have undergone radioisotopic synovectomy there be a low threshold for evaluation of malignancy.

### Expert opinion

Although significant strides have been made in the management of patients with haemophilia in the last few decades,
current therapy warrants improvement. Several different avenues are being approached for the improvement of the care of patients with this disorder. Clearly, the ultimate goal is to attain a cure. For this and other genetic disorders, this implies the advent of gene replacement/repair therapy. Although haemophilia is considered an ideal candidate for a disorder that can be cured through gene therapy [21], there have been numerous setbacks encountered in bringing this goal to reality. Although we do not doubt that safe and effective gene therapy will be realised in the future, there are still significant hurdles that must be overcome to assure that such an approach will be safe. Approximately 30 years ago, patients with severe haemophilia were promised a bright future, free of the devastating pain of joint bleeding, and the possibility to lead a relatively normal life with regular infusions of factor concentrates; only to develop a fatal infectious disease from the very factor that was treating their genetic disease. This lesson must not be forgotten when we attempt to cure this disease by manipulating DNA: the most complex of all biological molecules. The sobering reports of malignant transformation in children treated with gene therapy for severe combined immunodeficiency syndrome [28] will likely delay the widespread use of gene therapy; especially for haemophilia, a disease for which excellent therapy exists. We support the comments of Dr Giangrande in recommending that gene therapy trials in haemophilia be conducted only after safety has been demonstrated in diseases for which no other therapy exists such as muscular dystrophy and cystic fibrosis [74].

We do believe, however, that refinements in factor concentrates will become available in the relatively near future, which will lead to fewer inhibitor patients and more compliance with prophylactic regimens, respectively; thus further improving the outlook for patients with haemophilia.

Some clinical developments are currently impacting patient care. Attempting prophylaxis with the current factor products on a once-weekly basis has been effective in some patients and could be attempted in others, particularly those in whom a CVAD could be avoided by this approach. In order to expand this modality, the physiology and pharmacology of FVIII therapy must be better understood as the current pharmacokinetic data suggests that such therapy should not be fully effective. Another innovative area of research that is currently being explored is the use of adjunctive therapy for the management of joint disease. There is no doubt that inflammation plays a crucial role in the development of chronic joint disease in haemophilia. However, NSAIDs are relatively contraindicated, and glucocorticoids, although potentially effective, have too many long-term side effects to be a useful option. On the other hand, the COX-2 inhibitors may provide an excellent option as an adjunctive therapy for joint disease. They possess both anti-inflammatory and antiangiogenic properties that make them particularly attractive for the prevention of target joints. Current data are extremely limited. However, patients for whom painful arthritis without haemarthrosis is being managed with factor concentrates, a trial of a COX-2 inhibitor could be considered. Clearly, further research including randomised, placebo-controlled trials are the only way to prove efficacy and safety.

In conclusion, haemophilia has evolved from a life-threatening, crippling disease to one which has an excellent prognosis. Although therapeutic advances have made for a much improved quality of life for patients, further refinements of treatment can still further improve quality of life and ease of treatment. The ultimate goal is a cure, which undoubtedly will occur, though no one can predict for sure when it will be realised.

Bibliography
Papers of special note have been highlighted as either of interest (*) or of considerable interest (**) to readers.

   ** An excellent review of the history of haemophilia treatment.


   ** This perspective reviews the devastating infectious complications and should be read by all haemophilia treaters, especially those who are too young to have been in practice at the time.


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