Development of novel treatment options for patients with haemophilia

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Summary
Treatment of haemophilia has vastly improved over the last years, but many needs are still unmet. Baxter is continuously pursuing the aim to provide new therapeutic options to patients with haemophilia and to their treating physicians. In fact, there are several opportunities to improve existing therapies, e.g., by new indications for existing products, the introduction of new products, and by novel therapeutic approaches other than factor replacement. Among these, Baxter is working on a number of innovations, such as pharmacokinetics-tailored factor VIII prophylaxis, bypassing agent prophylaxis with FEIBA in inhibitor patients, development of a longer acting pegylated recombinant FVIII, a new recombinant factor IX, a new recombinant factor FVIIa, the first recombinant von Willebrand factor, recombinant ADAMTS13 (a disintegrin and metalloproteinase with a thrombospondin type 1 motif, member 13) as well as gene therapy to cure haemophilia B. Conclusion: Baxter is truly committed to the benefit for the patient, and therefore engaged in providing a more and more individualized treatment, in increasing efficiency of current products, in developing new products and new approaches with added value.

Schlüsselwörter
Hämophilie, Prophylaxe, lang wirkender Faktor VIII, Gentherapie

Zusammenfassung

The treatment of people with haemophilia has vastly improved since Judith Pool’s discovery in the first half of the 1960ies that coagulation factors can be concentrated by means of plasma cryoprecipitation (7, 8). The availability of FVIII concentrates opened up a whole new world in which people with haemophilia could effectively not only treat a bleeding episode when it occurred, but literally prevent it. FVIII concentrates allowed patients to treat themselves at home, thus decreasing their dependence on hospital care (11).

Today, long-term prophylaxis is considered the treatment of choice in children as well as adults with severe haemophilia (6).

The cloning of the factor IX gene in 1982 (2) and of the factor VIII gene (3, 12, 14) in 1984 subsequently led to the production of recombinant forms of factor VIII and IX (1, 16) by inserting the respective gene into a plasmid vector and transfecting mammalian cells with it. Three years later, the first infusion of recombinant factor VIII was given (15) in the USA.

Over the years, treatment options for patients with haemophilia have reached even higher standards with respect to safety and efficacy, e. g. the plasma-albumin-free production of recombinant factor VIII. However, there are still numerous opportunities to improve existing therapies, for example by finding new indications for existing products, by developing and introducing new products, and by innovative new therapeutic approaches other than factor replacement therapy.

All of these opportunities are pursued by Baxter to deliver more therapeutic options and better care to the patients.
Optimizing products

Our efforts towards innovation are aimed to answer unmet medical needs and to drive value for patients and their treating physicians; therefore we are exploiting innovative potential related to current products.

With the thorough evaluation of the pharmacokinetic properties of ADVATE, a prophylaxis dosing strategy can be tailored to the individual patients needs and aim to optimize doses and intervals between prophylactic infusions. A recent study (13) demonstrated the possibility to treat haemophilia A patients with ADVATE every third day (72 hours) with the same efficacy as standard prophylaxis with every other day regimen. In addition the study showed a decrease of the median annual bleed rate from 44 bleeds per subject and year during the on-demand therapy period to 1 bleed per subject and year while on one of the prophylaxis regimens. Of note, 42% of patients experienced no bleeding episode at all while on prophylaxis for one year.

Haemophilia A patients with inhibitors have been treated with the bypassing agent FEIBA either prophylactically or episodically. Baxter is carrying out a randomized clinical trial comparing the efficacy of FEIBA in on demand versus prophylactic use prompted by the observation in the independent PRO-FEIBA study (4) that prophylaxis with FEIBA in such patients was feasible, safe and effective. The PRO-FEIBA study showed that 85 U/kg of FEIBA given three times a week on three non-consecutive days was able to reduce the bleeding rate by 62% as compared with on-demand treatment. Specifically, during the 6-month on-demand period, subjects experienced a mean of 13.1 bleeding events versus a mean of 5.5 bleeding events during the prophylaxis period. The study, conducted in 34 patients, has confirmed and strengthened the evidence that FEIBA can reduce the bleeding rate by using 85 U/kg given three times a week on three non-consecutive days.

Developing new products

Baxter’s efforts to develop new products are aimed to add new therapeutic options to the existing ones. Therefore we have developed a recombinant FIX molecule for the management of haemophilia B. It is expressed in Chinese hamster ovary cells (CHO) with a plasma-albumin free manufacturing process. This new rFIX product has already undergone extensive characterization of its safety and efficacy in preclinical and toxicological studies and has demonstrated comparability with an existing and licensed rFIX. Clinical phase 1–3 studies have been completed and data were submitted for regulatory approval to the US Food and Drug Administration (FDA) in August 2012 and were presented at the annual Congress of the American Society of Hematology (ASH) in December 2012. The submission for licensure in the European Union still requires a study in children to be conform with the European Medicine Agency (EMA) requirements.

For the treatment of patients with von Willebrand’s disease (VWD) a recombinant von Willebrand factor (rVWF) is currently studied in a phase 3 clinical trial. It represents the largest and most complex recombinant protein developed to date and the first and only recombinant VWF currently in use in humans.

Using the same plasma-albumin free manufacturing platform we have also developed a recombinant activated factor VII (rFVIIa) molecule expressed in CHO cells for the treatment of bleeds in patients with inhibitors against FVIII or FIX. Its comparability with the licensed rFVIIa product has already been established in pre-clinical and toxicological studies. In a transgenic mouse system expressing human FVII this new rFVIIa did not induce anti-FVII inhibitor development. A clinical phase I/II study has been completed and data evaluation is ongoing. A phase III clinical trial was initiated in early 2013.

For the optimization of prophylaxis in patients with haemophilia A we are working on a longer acting rFVIII that is currently tested in a phase III clinical trial. This product, which is based on our efficacious and safe ADVATE platform, extends the half-life of ADVATE through the attachment of a water soluble polymer (polyethylene glycol, PEG), thereby possibly extending the dosing interval beyond every third day for prophylaxis of bleeding in patients with haemophilia A.

This long acting rFVIII has been demonstrated to preserve the immunogenic tolerance in a transgenic mouse system expressing human FVIII. A phase I/II clinical trial has been completed with two cohorts:

- 8 patients who received 30 IU/kg and
- 10 patients treated with 60 IU/kg.

Data will become available soon.

Entering the future

The ultimate goal in a chronic hereditary disease like haemophilia is – without any doubt – to cure this illness. In order to get closer to this visionary goal, Baxter has established a collaboration with Chatham Therapeutics with the aim to develop a gene therapy for patients with haemophilia B. Nathwani et al. (5) have conducted a successful proof-of-concept study using a FIX transgene in an adeno-associated virus. Our gene therapy approach utilizes the capsid of an adeno-associated virus type 8 (AAV8), which has a low seroprevalence in humans and promotes a selective delivery to the liver. Our technology also employs a self-complementary genomic form, which enhances the gene expression with a rapid formation of stable double stranded linear molecules in target tissues. It contains a liver specific transathyrein enhancer-promoter, which increases hepatic transgene expression. The transfected FIX gene is a variant transgene with the hyperactive FIX variant (R338L) (10) later found in a patient in Padua, Italy (9). This gain of function mutation leads to a FIX protein with almost 8-fold higher specific activity compared to wild type FIX. As a consequence even modest FIX antigen expression levels may generate substantial FIX activity in the patients’ plasma. In addition, the FIX gene has been codon-optimized to improve mRNA stability and translation. The Investigational New Drug application (IND) has been filed with competent authorities and has been accepted;
consequently a phase 1 clinical trial has been initiated.

In addition, we are developing a recombinant form of ADAMTS13 – the cleavage enzyme for von Willebrand factor – for the treatment of patients with thrombotic thrombocytopenic purpura (TTP) who are lacking this enzyme. It is highly active under physiological (shear dependent) conditions and efficacious in an animal model that closely mimics the situation in patients with hereditary TTP. In prophylactic treatment in the animal model, all doses led to a reduction in incidence and/or severity of TTP-related findings, while in a therapeutic setting in the animal model, treatment with rADAMTS13 mitigated the disease symptoms in a treatment interval-dependent manner. All preclinical pharmacology/toxicology studies have been completed.

Conclusions

Baxter has a legacy of six decades that demonstrates our commitment in putting the patient at the centre of our strategy, aiming to provide a more individualized treatment, enhancing the safety and efficacy of current products, developing new products with added value, and giving innovative answers to unmet medical needs.

Conflict of interest

The authors are full time employees of Baxter Innovations GmbH, Global R & D and Medical Affairs Bioscience, Vienna, Austria and Westlake Village, California, USA.

References