At a dedicated symposium held in Johannesburg recently to celebrate 30 years of research with rFVIIa, Dr Karin Knobe, Associate Professor, Lund University, Sweden and Global Development Specialist, Haemophilia Medical and Science Division, Novo Nordisk, described the product’s clinical development and future possibilities.

**30 years of research with rFVIIa**

At the beginning of her presentation, Dr Knobe pointed out that up to 20-30% of haemophilia A and B patients will develop inhibitors against the factor they are missing (20-33% of haemophilia A and 1-6% of haemophilia B patients develop inhibitors). In the 1970s, treatment options for joint bleeding (haemarthroses) in these patients were limited to the use of either higher doses of factor VIII combined with extracorporeal adsorption of inhibitors or administration of plasma-derived activated....

**KEY MESSAGES**

- Recombinant factor VIIa (rFVIIa) therapy has improved the quality of life and outcomes of haemophilia patients with inhibitors (neutralising antibodies to factor VIII or factor IX), allowing them to achieve a quality of life similar to that of haemophilia patients without inhibitors.
- The launch in South Africa of a new delivery system for rFVIIa, the pre-filled factor VIIa syringe, provides a fast and simple reconstitution process enabling patients to reach the target of treating their bleeds within two hours.
- Clinicians in South Africa need to have a higher index of suspicion when young boys with swollen and bruised joints are seen in trauma units as some 50% of patients with haemophilia (mostly mild and moderate) in South Africa are currently not diagnosed.
- Treatment of people with haemophilia should be supervised by a Haemophilia Comprehensive Care Centre (HCCC) in collaboration with the patient’s primary care practitioner. There are currently 16 HCCC sites throughout South Africa (details available on the South African Haemophilia Foundation website www.haemophilia.org.za).
- The guidelines for the treatment of haemophilia in South Africa are currently being revised by the Medical and Scientific Advisory Council (MASAC) of the South African Haemophilia Foundation with a view to placing a greater emphasis on prophylaxis in order to maintain factor activity, reduce the frequency of bleeds and prevent musculoskeletal complications of the disease.
- In South Africa, the current experience is that approximately 10-20% of haemophiliac patients will develop inhibitors and depending on the extent of inhibition will require bypassing agents (rFVIIa or aPCC (FEIBA®)) for managing bleeding episodes. In Europe, 30% of haemophiliac patients develop inhibitors.
- Awareness of acquired haemophilia (AH), although it is a rare condition, is key for general practitioners and specialists (e.g. gynaecologists and oncologists). AH should be considered in a bleeding patient without a personal or family history of bleeding disorders. Appropriate laboratory tests rapidly confirm the diagnosis.
Optimising haemophilia care

prothrombin complex concentrates (pd-aPCCs). The pd-aPCC therapies, including the factor VIII inhibitor bypassing activity (FEIBA or anti-inhibitor coagulant complex) achieved efficacy levels of 50-65% in controlled clinical trials, but were still associated with thrombogenic risks, while the level of orthopaedic complications in haemophilic patients with inhibitors remained higher than in non-inhibitor patients. “Treatment gaps between inhibitor and non-inhibitor patients therefore remained,” Dr Knobe noted.

The potential of plasma-derived factor VIIa as a therapeutic agent was recognised in the mid-1970s and was used successfully to induce haemostasis in patients with haemophilia and inhibitors in 1981/1982 without formal clinical trials. The advent of HIV and advancing recombinant technology led to the official start of the clinical programme on recombinant factor VIIa (rFVIIa) at Novo Nordisk, using baby hamster kidney cells to produce recombinant product. Phased clinical trials started in 1989. These clinical trials established the efficacy of rFVIIa in haemophilia (Table 1). 3-6 It is now regarded as first-choice therapy in patients with inhibitors, although pd-aPCC therapies are not significantly inferior when it comes to bleeding control. Some patients tend to respond to one but not the other agent. Thrombotic risk is lower with rFVIIa. The mechanism of action of rFVIIa is summarised in Table 2 and, importantly, these actions occur in a tissue-factor independent manner, thereby avoiding the development of antibodies to factor VII. 7-9

These clinical studies led to registration of rFVIIa worldwide and in South Africa in 2007 with the following clinical indications for use: (a) congenital haemophilia with inhibitors to coagulation factor VIII and factor IX; (b) congenital factor VII deficiency; (c) Glanzmann’s thrombasthenia; and (d) acquired haemophilia (AH) patients undergoing surgery or invasive procedures.

Improvements to rFVIIa continue; these include the introduction of a pre-filled syringe, which provides patients with easy-to-use rapid bleeding control.

Improving the clinical use of rFVIIa

Dr Yagalen Naidoo, clinical haematologist at Grey’s Hospital, KwaZulu-Natal, noted that it was vital to choose the right dose of rFVIIa and place of administration (home versus hospital), as well as to minimise the time to treatment in the event of a spontaneous or causal bleed in a haemophilic patient.

The use of a bypassing agent should, however, be based on patient experience with the agent. “While the cost of rFVIIa is an important factor, we need to consider the true cost of treating a bleeding event, taking into account the total direct cost needed to achieve resolution of the bleed (drug cost, efficacy, dose regimen), time to achieve bleed resolution and the need to retreat a patient following a re-bleed,” Dr Naidoo pointed out.

Assessing treatment effectiveness from published data is key to determining costs and benefits, reflected by the absolute risk reduction (ARR) and the number needed to treat (NNT) to achieve desired benefit. Dr Naidoo selected key data from rFVIIa trials to illustrate the selection of time and dosage:

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“The advent of rFVIIa in the mid-1980s provided an effective and safe treatment option for haemophilia patients with inhibitors (antibodies) for the first time.” Dr Karin Knobe, Sweden

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Table 1. Development of rFVIIa

| • 90–100% efficacy in major surgery |
| • 90–100 µg/kg q2 hours for at least 24 hours |
| • 93% efficacy in controlling bleeding episodes at 12 hours |
| • Most patients require more than one dose of 90µg/kg |
| • 92% efficacy in joint bleeds (home treatment) |

Table 2. What does rFVIIa do?

| rFVIIa enhances thrombin generation on thrombin-activated platelets at the site of injury |
| rFVIIa induces a tighter structure in fibrin clots formed from factor VIII- and factor IX-deficient plasma at the site of injury |
a) Doses less than 200µg/kg versus more than 200µg/kg
In an evaluation of dosages, given mainly at home to stop/limit bleeds, the UK Haemophilia and Thrombosis Society Registry\textsuperscript{10} showed that doses above 200µg/kg increase efficacy with an ARR of 13% and NNT of 7.7 haemophilia patients with inhibitors. The median total dose given over 72 hours was 360µg/kg.

b) Time-to-treatment: less than two hours versus more than two hours
Using a Czech registry, dosage and time-to-treatment with rFVIIa was evaluated in haemophilic patients with high-responding inhibitors. The study\textsuperscript{11} analysed ‘real-life’ clinical data and focused on collecting the same parameters in different patients (a total of 128 bleeds were evaluated). In principle, patients treated within two hours of bleeding onset experienced less re-bleeding than patients treated after two hours. Patients who were treated later, experienced fewer re-bleedings when a higher dose of rFVIIa (>250µg/kg) was used.\textsuperscript{11}

c) Home rFVIIa therapy versus pd-aPCC therapy
This study evaluated the efficacy and safety of rFVIIa versus pd-aPCC for controlling joint bleeds in a home-treatment setting; specifically comparing the dose of 3x90µg/kg rFVIIa versus the 270µg/kg single dose and pd-aPCC. The percentage of rFVIIa-treated patients (270µg/kg and 3x90µg/kg group) requiring additional haemostatics within nine hours was lower than in the pd-aPCC group.\textsuperscript{12}

In a further discussion of dosages in emergency care, Dr Naidoo stressed the principle that when a haemophilic patient with inhibitors arrives late with a joint bleed, the larger dose of 270µg/kg of rFVIIa should be initiated and the response re-assessed after six hours. The follow-up dose on continued bleeding should be based on the emerging clinical picture.

Preserving joint and musculoskeletal health – early therapy and prophylaxis are key to limiting arthropathy
Dr M Morfini, Italy, pointed out that most bleeding episodes in haemophilia affect the joints (65-85%), with most occurring in the hinged joints – knees, ankles and elbows. Bleeding episodes also affect the multi-axial joints such as the hips and shoulders, but less frequently. The effects of joint bleeds include pain, swelling, warmth and muscle spasm while recurrent bleeding causes joint damage, deformity and crippling (Figure 1).

Figure 1. The mechanism of blood-induced joint damage
Deterioration of joints happens gradually and patients with inhibitors are often worse off. Interventions such as synovectomy or surgery greatly increase the subsequent costs of haemophilia treatment and dramatically affect quality of life.

“While MRI is the gold standard for assessing joint health, ultrasound is also very useful in the South African situation as it visualises soft tissues and cartilage, which together with clinical assessment, can guide the multidisciplinary team’s intervention strategies,” Dr M Morfini concluded.

The use of recombinant activated factor VII in patients with AH

AH is a rare, often severe bleeding disorder caused by the spontaneous development of autoantibodies to coagulation factor VIII. The cause of AH is idiopathic in 50% of cases, with the remainder consequent on a variety of physiological or pathological conditions, such as connective tissue disease, malignant tumours, pregnancy, childbirth, drugs and aging. Patients with AH tend to be elderly and have underlying comorbidities. Bleeding in AH is spontaneous (68%) or related to trauma (32%), with bleeding in the skin, mucous membranes, muscle and soft tissue being more common than intra-articular bleeds.

More than two-thirds of bleeds are severe, with severity not correlated with factor VIII level or inhibitor titre at diagnosis. Bleeding-related mortality ranges from approximately 3% to 22%.

Treatment aims to control acute bleeds (haemostatic therapy) and to eradicate autoantibodies (immunotherapy). First-line haemostatic therapy involves the use of bypassing agents, including rFVIIa and pd-aPCC. rFVIIa overcomes the action of inhibitory autoantibodies by directly activating coagulation factor X on the surface of activated platelets and at the site of injury and therefore bypassing factor VIII and factor IX.

A pertinent recent report based on two emergency and compassionate use programmes, four patient registries and a post-marketing study, published between 1997 and 2014, provides useful clinical insights (Table 3).

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<tr>
<th>Table 3. Key outcomes reflecting efficacy of rFVIIa in acute bleeds</th>
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<td>• Reported average dose of rFVIIa was approximately 90µg/kg.</td>
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<td>• Effective bleeding control ranged from 48% to 100%.</td>
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<td>• Overall bleeding control (effective or partially effective) ranged from 81% to 100%.</td>
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<tr>
<td>• In one study, bleeding control with rFVIIa was comparable to that in patients treated with pd-aPCC therapy.</td>
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<td>• In one study, percentage bleeding control was higher when rFVIIa was used as first-line vs salvage therapy.</td>
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rFVIIa was shown to be safe, with thromboembolic events (TEs) reported in one patient registry; they occurred in five of 174 (3%) patients receiving rFVIIa and three of 63 (5%) patients receiving pd-aPCC therapy. In the post-marketing study, only three patients experienced TEs that were considered to be related to rFVIIa treatment. All three patients were elderly with significant comorbidities.

In patient registries and surveillance studies, deaths reported from infection or side effects of immunosuppressive therapy ranged from 4.2% to 16%. (Death due to bleeding was found to be 3.5%-9.1% in recent patient registries.)

In conclusion, combined data from emergency and compassionate use programmes, patient registries and a post-marketing study show that rFVIIa is the most rigorously reported haemostatic agent used to control bleeding in patients with AH. It provides a high and consistent rate of haemostatic efficacy and is regarded as first-line treatment for AH patients in a wide range of surgical and non-surgical bleeding situations.
References