Health technology description

Recombinant human activated factor VIIa (rFVIIa) is licensed as NovoSeven® in Europe for promoting haemostasis in people who have haemophilia with antibody inhibitors to coagulation factors VIII or IX and for treatment of congenital factor VII deficiency and Glanzmann’s thrombasthenia\(^1\). Specifically, it is used for: the management of bleeding in haemophilia A and B; for minor and major haemorrhage if inhibitor levels are too high for satisfactory levels of deficient clotting factor to be achieved; and in patients undergoing surgery. This Evidence Note considers only the use of rFVIIa in adults and children with haemophilia who develop inhibitors; in practice, the choice of treatment for bleeding in patients with inhibitors is determined by several factors including the severity of the bleed, the level of inhibitor and history of previous exposure to plasma derived blood products\(^2\).

Epidemiology

Haemophilia is a disorder which impairs the body's ability to control bleeding. It is due to a defect in the coagulation mechanism which can be either inherited or acquired. Approximately 6,000 people in the UK are affected by congenital haemophilia [www.haemophilia.org.uk] and acquired haemophilia affects 1.34 per million population per year\(^3\). Haemophilia A and B are X-linked and recessive, and therefore far more common among males than females. The two types of haemophilia (A, accounting for 80% of cases and B which accounts for 20%) are caused by a deficiency in coagulation factors VIII and IX, respectively. Both conditions result in the same phenotype which is determined by the residual coagulation factor levels. The majority of the morbidity of the untreated disease is musculoskeletal due to recurrent haemarthrosis and muscular haematoma. Treatment is not curative but instead controls the disorder. Two options are available. Previously, treatment was on demand for the management of acute bleeding episodes, but the modern management of new patients with haemophilia is by prophylaxis which aims to maintain coagulation factor levels above 1% of the normal level\(^4\) as this effectively prevents spontaneous haemorrhage. There is good evidence for this approach using factor VIII and IX concentrates\(^5\). Unfortunately, the most common serious adverse effect of using presently available concentrates is the development of inhibitory antibodies (inhibitors) directed against the coagulation factor being infused. This is far more common in recipients of factor VIII concentrates than factor IX concentrates. The development of inhibitors results in refractoriness to concentrate infusion. This is managed in the short term by treating bleeding episodes using products which facilitate coagulation by pathways which are independent of factor VIII and/or IX. Long term, this is achieved by attempting to abolish inhibitor production through the induction of immune tolerance.
Clinical effectiveness

Recombinant factor VIIa has been established for some time as a useful treatment of bleeding in haemophilia with inhibitors. The United Kingdom Haemophilia Centre Doctors Association (UKHCDO) guideline, last revised in 2006, states that a dose of 90 µg/kg rFVIIa has been shown to control 70–100% of bleeding episodes. An up-to-date review reports that the standard dose is considered to be 90–120 µg/kg given as a bolus every 2–3 hours until cessation of bleeding, however there is considerable variation in dosing levels, intervals and duration of treatment among practitioners. The report does not speculate on the reasons for this variation.

Some practitioners use doses of rFVIIa above 90 µg/kg (the dose recommended by manufacturers), although there are few dose finding studies. A recent RCT compared 90 µg/kg every three hours as required with a single dose of 270 µg/kg. Both regimens controlled joint bleeding equally and the median amount of rFVIIa used per successful treatment course was identical (270 µg/kg). The authors concluded that the advantage conferred by a single high dose was convenience, particularly in patients with difficult venous access and in haemorrhages into target joints where rapid reversal of bleeding is important. Higher efficacy and quicker resolution of joint bleeds have been reported with single bolus doses greater than 200 µg/kg but further clinical trials comparing 90 µg/kg with 300 µg/kg are required.

Although originally developed for the treatment of inhibitor complicated haemophilia, the literature shows that rFVIIa is being used increasingly in indications for which it is not licensed. However, a recent review suggests that the majority of other indications where randomised controlled studies have been performed show almost no evidence of a benefit.

Recent case reports of the use of rFVIIA as prophylaxis in patients with inhibitors have been published. There is little substantive evidence for this practice and it is likely that the publication of these reports is associated with a strong bias towards reporting of positive outcomes.

Economic implications

Factor VIIa has a short half-life, meaning that it is rapidly cleared. In general, this means that numerous injections are required to maintain adequate haemostasis especially in patients with inhibitors. As a result, treatment is very costly if administered over a prolonged period. For example, the cost of four doses for a 10 kg baby or 90 kg adult male would be £2,237.71 or £20,139.35, respectively. This assumes that treatment of an acute bleeding episode uses an average of four doses of rFVIIa at 90µg/kg/dose, not allowing for wastage of partly used vials, at the NHS List Price in June 2007 of £1,269.62 + VAT per 2.4 mg pack.

Further information

For further information about the Evidence Note process, see www.nhshealthquality.org

To propose a topic for an Evidence Note, email evidencenotes@nhshealthquality.org

References can be accessed via the e-library (www.elib.scot.nhs.uk), or by contacting your local library and information service.

Safety

Overall, the safety profile of rFVIIa is good, with doses of up to 346 µg/kg being reported as well tolerated. It is associated with a low risk of thromboembolic events, the incidence of which is higher when rFVIIa is used off licence.
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Equality & diversity

NHS QIS is committed to equality and diversity. This document, and the research on which it is based, have been assessed for any likely impact on the six equality groups defined by age, gender, race/ethnicity, religion/faith, disability and sexual orientation. For a summary of the equality and diversity impact assessment, please see http://www.nhshealthquality.org/nhsqis/files/EQIARIA0052.pdf

References