Recombinant Factor VIIa Concentrate versus Plasma-derived Concentrates for the Treatment of Acute Bleeding Episodes in Persons with Haemophilia and Inhibitors

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Abstract

The development of inhibitors remains the most challenging complication of treatment in persons with haemophilia, resulting in increased morbidity and a significant economic burden. The ultimate goal of treatment in patients with inhibitors is immune tolerance induction (ITI) therapy; however, during the induction phase of ITI, when ITI fails and where ITI is not affordable, the treatment of bleeding becomes a crucial issue. Recombinant activated factor VII (rFVIIa) and activated prothrombin complex concentrate (aPCC) have been developed to bypass the inhibitor antibody effect and have been tested in several randomised controlled trials, including two crossover head-to-head comparisons. Two systematic reviews of the literature have appraised and synthesised the available evidence. The recombinant drug seems to provide a more favourable benefit–risk ratio and may be easily administered as a single front-loaded bolus, making it a good candidate for the role of first-line treatment for bleeding in patients with inhibitors. Aggressive treatment of acute bleeds should be considered, including the use of higher and repeated-dose regimens until complete resolution of the bleed.

Keywords

Haemophilia, inhibitors, bypassing agents, acute bleeding

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Persons with haemophilia (PWH) experience spontaneous or trauma-related bleedings, most commonly joint bleeds, which progressively lead to swelling, limitation of movement, cartilage destruction and haemophilic arthropathy.[1] Regular replacement therapy with clotting factor concentrates significantly improves the quality of life in PWH, dramatically reducing the bleeding rate and preserving the joint health status.[2,3] The development of inhibitors remains the most challenging complication of treatment in PWH, resulting in increased morbidity and a significant economic burden.[4] Inhibitors can be classified as high- or low-responding according to a cut-off level of 5 Bethesda units (BU). The likelihood of developing inhibitors is highest during the first 50 exposure days (EDs) to clotting factor, and searching for inhibitors every three to five EDs for the first 20 EDs and monthly until 50 EDs is recommended for early detection.[5] Many low-level inhibitors will disappear spontaneously (transient inhibitors),[6] while others persist, sometimes at very high titre, making standard replacement treatment with factor VIII (FVIII) ineffective. The prevalence of inhibitors has been found to be 5–7% in all severities[7] of haemophilia A and up to 30% in patients with severe haemophilia.[8] In patients with severe haemophilia B the prevalence of inhibitors is around 3%.[8]

The ultimate goal of treatment in patients with inhibitors is immune tolerance induction (ITI); however, during the induction phase of ITI, when ITI fails and where ITI is not affordable, the treatment of bleeding becomes a relevant objective. The goals in the treatment of bleeding episodes are to relieve pain and to prevent, or at least slow down, the progression towards arthropathy caused by recurrent bleeding into the joint. Aggressive treatment of acute bleeds should be considered, including the use of higher and repeated-dose regimens until complete resolution of the bleed.[9,10]

For patients with high-responding, high-titre inhibitors and acute bleeding, bypassing agents – recombinant activated factor VII (rFVIIa) and plasma-derived activated prothrombin complex concentrate (aPCC) – are the gold standard.[7,8] The use of bypassing agents in the management of patients with inhibitors in different European countries has recently been assessed by Astermark et al.[11] who ran a survey among investigators from 22 large haemophilia centres participating in the European Haemophilia Therapy Standardisation Board (EHTSB) network. The centres collectively followed 381 haemophilia patients with inhibitors to FVIII (349 patients) or factor IX (FIX) (32 patients), of whom 72% had high-responding inhibitors. In 10 of the centres high-dose FVIII/FIX was used as the first option for low-responding inhibitor patients. rFVIIa was routinely used in all centres for both children and adults at a dosage ranging from 90 to 250µg/kg every two to four hours. aPCC was used in 85 and 40% of the centres in adults with

haemophilia A and B, respectively, and in 25 and 15% of the centres in children with haemophilia A and B, respectively, at a dosage of 50–100IU/kg every six to 12 hours. Higher dosages of both agents were considered in case of life-threatening bleeds. Eight of the 22 centres perform prophylactic treatment with bypassing agents during ITI. Six of these centres use either aPCC or rFVIIa, one centre only rFVIIa and the other only aPCC. In patients failing an ITI course, a new attempt would be considered by 17 of 21 centres (81%) and 11 of these centres (52%) would also consider prophylactic treatment with bypassing agents. Six of these centres use either aPCC or rFVIIa, one centre rFVIIa only and another aPCC only. In patients failing an ITI course, a new attempt would be considered by 17 of 21 centres (81%) and 11 of these centres (52%) would also consider using prophylactic treatment with bypassing agents. aPCC or rFVIIa would be considered for prophylaxis, whereas six centres (55%) would only use rFVIIa for this indication. Overall, both agents were reported to have an efficacy rate of approximately 80% at six hours (as assessed by patients' reports and by cases needing a subsequent dose of the drug).

Evidence of Efficacy

There are several literature reports about the efficacy and safety of bypassing agents for treatment of bleeding in haemophilia patients with inhibitors. The evidence base has been systematically reviewed using two approaches by Iorio et al.[12] and Treur et al.[13]

Iorio et al. summarised the evidence from the two available head-to-head crossover multicentre randomised controlled trials,[14,15] concluding that rFVIIa and aPCC were found to be similar in efficacy and in carrying a low risk of thromboembolic complications. Both drugs can be administered as a single intravenous bolus (270µg/kg rFVIIa, 75–100IU/kg aPCC). Other non-randomised evidence can be usefully taken into account in tailoring to the patients the more appropriate treatment in clinical practice. Sixty-six PWH were enrolled from 27 centres in Europe and North America by Astermark et al. in the FEIBA–NovoSeven Comparative (FENOC) study.[14] The aim of the trial was to show the equivalence of rFVIIa and aPCC in treating ankle, knee and elbow joint bleeding, assessing the reported efficacy of each of the drugs. To demonstrate equipotency of the drugs, a classic non-inferiority design, with an acceptable difference of no more than 15%, was adopted. The primary outcome was the patient's self-assessment six hours after drug administration. Data for 96 bleeding episodes in 48 participants were analysed. The criteria for declaring the agents equivalent at six hours were not met: the confidence interval of the ratio of their geometric mean efficacies slightly exceeded the 15% boundary (11.4–15.7%) (p=0.059). aPCC and rFVIIa appeared to exhibit a similar effect on joint bleeds, although a substantial proportion of patients rated the efficacies of the agents differently. Bleeding episodes in the aPCC and rFVIIa arms received only one (63.6%) and one or two (92.3%) infusions, respectively. The trial by Young et al.[15] compared the efficacy and safety of rFVIIa and aPCC in controlling joint bleeds in a home-treatment setting. Patients randomly received each of three treatments in one of six possible sequences: 270µg/kg rFVIIa at hour 0 + placebo at hours 3 and 6; 90µg/kg rFVIIa at hours 0, 3 and 6; and 75IU/kg aPCC at hour 0, possibly repeated at hour 12. Efficacy was assessed by the requirement for additional treatment within nine hours and by an *ad hoc* global response algorithm. The percentage of patients requiring additional haemostatics within nine hours was lower for rFVIIa 270µg/kg^{-1} (8.3%) and for rFVIIa 90µg/kg^{-1} every three hours (9.1%) than for aPCC (36.4%) with a p value of 0.032 and 0.069 when compared with rFVIIa 90mcg versus aPCC and rFVIIa versus aPCC 270mcg, respectively. Both rFVIIa treatment groups showed similar use of rescue medication (8.3 and 9.1% of episodes). No significant differences in treatment response were observed with the global response algorithm (p=0.173). No safety concerns were identified.

Treur et al.[13] provided a comprehensive appraisal of all the available randomised and non-randomised evidence from 17 studies and 382 patients treated with rFVIIa and 317 treated with aPCC,[11,15–24] using a Bayesian approach to predict the likelihood of response 12, 24 and 36 hours after three-hourly 90µg/kg rFVIIa or 75IU/kg aPCC. The results showed rFVIIa to be the dominant strategy with a 66, 88 and 95% likelihood of response, respectively, the results being consistent at several sensitivity analyses.

The feasibility of front-loaded treatment with 270µg/kg rFVIIa was further demonstrated by Kavakli et al.[20] and Santagostino et al.[22] Patients were randomly allocated by Kavakli et al.[20] to have a first joint bleeding episode treated with one 270µg/kg rFVIIa dose followed by two doses of placebo at three-hour intervals and a second joint bleed with three single doses of 90µg/kg rFVIIa at three-hour intervals, or vice versa. Treatment was rated as effective for 65% of patients using the 270µg/kg dose versus 70% for the three × 90µg/kg regimen.

Santagostino et al.[22] enrolled 20 PWH in a randomised crossover trial comparing a standard dose of rFVIIa (90µg/kg every three hours) with a single high dose of 270µg/kg. Patients who did not improve within nine hours received an additional standard dose of rFVIIa. Thirty-two and 36 haemarthroses were treated in the standard group and the high-dose group, respectively. Seventy-one per cent of these bleeds occurred in target joints. Santagostino et al. found a similar success rate for both treatment arms (31 and 25% at nine hours, 53 and 50% at 24 hours, and 66 and 64% at 48 hours for standard dose and high dose, respectively).

Treatment of bleeding with either rFVIIa or aPCC proved to be safe and well tolerated. The FENOC study did not report any study-related or drug-related adverse effects. The trial by Young et al. did not report any thrombotic, fatal or clinical laboratory adverse events; however, recorded 32 treatment-emergent adverse events in 14 participants. Of these, three were in the rFVIIa 270µg/kg group, five were in the rFVIIa three × 90µg/kg group and six were in the aPCC group. No adverse event was considered to be related to the study drug.[12,14,15]

Two disadvantages of aPCC are the lower safety profile as far as blood-borne infections are considered and the likelihood of inducing an anamnestic response due to the traces of FVIII that it may contain.

Conclusion

The systematic appraisal of the available evidence showed that most bleeding episodes in haemophilia patients with inhibitors can be successfully treated with rFVIIa or aPCC. The recombinant drug seems to provide a more favourable benefit–risk ratio and may be easily administered as a single front-loaded bolus, making it a good candidate for the role of first-line treatment for bleeding in patients with inhibitors. ■

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