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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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,13,15 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 most 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 boundary 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 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 efficacies of the agents differently. Bleeding episodes in the aPCC group. No adverse event was considered to be related to the study drug.13,14,15

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 events. 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.13,14,15

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.
Haemophilia