Efficacy of Bypassing Agents in Patients With Hemophilia and Inhibitors: A Systematic Review and Meta-Analysis

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ABSTRACT

Background: Activated prothrombin complex concentrate (aPCC) and recombinant Factor VIIa (rFVIIa) are 2 bypassing agents commonly used for treating acute bleeds in hemophiliac patients with inhibitors. A wide range of efficacy rates for aPCC and rFVIIa have been reported in a number of single-armed and randomized controlled comparative studies.

Objective: The aims of this study were to compare the clinical efficacy of aPCC and rFVIIa using a classic meta-analytic approach and to explore the role of study characteristics as covariates in a meta-analysis of previously published clinical studies in hemophiliac patients with antibodies to the missing Factor VIII or IX.

Methods: A systematic search was conducted to identify studies on the efficacy of aPCC and rFVIIa 90 and 270 μg/kg for treating joint bleeds. The efficacy rates with aPCC and rFVIIa were pooled separately, assuming fixed or random effects. Subgroup analyses were conducted to pool the efficacy rates for bleeds evaluated at 8–12, 18–27, and 36–72 hours after the start of the initial infusion. Meta-regression was used to investigate the association between pooled efficacy rates and study characteristics.

Results: Although only 2 studies directly compared the efficacy of aPCC and rFVIIa, data from ~2392 joint bleeding episodes from 19 studies were included. The pooled efficacy rates were 80.8% with aPCC and 68.4% with rFVIIa (90 μg/kg, 72.0%; 270 μg/kg, 55.7%). The pooled efficacy rates with aPCC at 8–12, 18–27, and 36–72 hours were 49.2%, 70.2%, and 90.9%, respectively. The corresponding pooled rates with rFVIIa 90 μg/kg were 66.6%, 70.7%, and 77.7%. No significant differences were found between the pooled efficacy rates with aPCC and rFVIIa overall or at any of the time points evaluated. Positive associations were found between reported efficacy and duration of follow-up and the number of bleeds evaluated.

Conclusions: Given the paucity of high-quality studies, the findings from the present review and meta-analysis suggest no conclusive evidence that aPCC or rFVIIa is significantly more efficacious than the other in the treatment of joint bleeding episodes in hemophiliac patients with inhibitors. (*Clin Ther*. 2012;34:434–445)

Key words: aPCC, efficacy, hemophilia, inhibitor, meta-analysis, rFVIIa.

INTRODUCTION

The optimal use of clotting factor concentrate is essential for preventing the long-term complications of bleeding, such as joint and muscle damage, in patients with hemophilia.[1,2] However, ~20% to 35% of patients with severe hemophilia A and 4% to 6% of those with severe hemophilia B develop antibodies to the missing Factor VIII or IX during factor-replacement therapy.[3–5] The development of antibodies presents a distinct clinical and economic challenge to bleed management in such patients. In patients with low-level (≤5 Bethesda units [BU]) inhibitors, bleeds generally can be managed with escalating doses of clotting factor to overwhelm the inhibitor level and to achieve hemostasis.[6] However, in the presence of high-level (>5 BU) inhibitors, bypassing therapy with activated prothrombin complex concentrate (aPCC*) or recombinant Factor VIIa (rFVIIa†) may be needed.[7,8]

aPCC and rFVIIa have different mechanisms of action, and the efficacy of each agent varies among individuals.[9] In accordance with the manufacturer's package insert,[10] the recommended dosage by weight of aPCC infusion is 50 to 100 IU/kg q6–12h, up to 200

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*Trademark: Feiba™ (Baxter AG, Vienna, Austria).

†Trademark: NovoSeven® (Novo Nordisk A/S, Bagsværd, Denmark).

IU/kg/d. The dosage of rFVIIa approved by the US Food and Drug Administration (FDA) is 90 μg/kg. A single dose of 270 μg/kg was approved by the European Agency for the Evaluation of Medicinal Products in 2007.

There is no objective laboratory test for monitoring the efficacy of bypassing products; improvement of outcomes is evaluated based on the cessation of bleeding and/or efficacy ratings that take into account both a clinical assessment of range of motion and self-reported pain. No single agent is efficacious in all patients or all bleeding episodes. Patients who fail to respond to rFVIIa may respond to aPCC and vice versa. Teitel et al[11] recommended that nonresponders to 1 agent be switched to the other agent.

The efficacy and safety profiles of aPCC and rFVIIa have been studied in a number of single-armed and comparative randomized controlled trials (RCTs). In single-armed studies, both agents were reported to be efficacious (80%–90%) and generally well-tolerated in the treatment of acute bleeds in hemophiliac patients with inhibitors.[12–14] Recently, 2 head-to-head RCTs compared the efficacy and safety profiles of aPCC and rFVIIa.[15,16] The FENOC (Feiba NovoSeven Comparative) study[15] compared the efficacy of aPCC 75 to 100 IU/kg and rFVIIa 90 to 120 μg/kg using an equivalence design. Patient-rated effective response and cessation of bleeding were similar with both drugs over the course of the 48-hour follow-up period. The differences in efficacy rates failed to reach the predetermined levels of clinically acceptable magnitude for statistical equivalence. Neither product was reported to have efficacy superior to that of the other in terms of bleeding cessation rate at any time point. The other head-to-head RCT, by Young et al,[16] compared the efficacy of 1 dose of aPCC 75 IU/kg to that of 3 infusions of rFVIIa 90 μg/kg or a single bolus of rFVIIa 270 μg/kg. Outcomes were measured using a global efficacy algorithm that took into account pain and mobility scores at 9 hours after the start of infusion and the requirement for additional hemostatic agents (rescue medication) within 9 hours after the start of infusion. No statistically significant differences were found in the global algorithm ($P = 0.173$) or in pain and mobility scores measured separately ($P = 0.219$ and $P = 0.903$, respectively). Although a significantly lower percentage of patients in the rFVIIa 270-μg/kg group required rescue medication compared with the aPCC group ($P = 0.023$), the difference in rescue medication use between the aPCC group and the rFVIIa 3 × 90-μg/kg group was nonsignificant ($P = 0.069$). However, the follow-up period was not long enough to demonstrate the complete bleeding cessation rate, and the statistical power was relatively low due to a high dropout rate.

Based on the findings from those 2 RCTs,[15,16] the Cochrane Collaboration conducted a review and reported that there was no conclusive evidence that the efficacy of 1 product was superior to that of the other.[17] In a study that used a Bayesian meta-analytic approach, data from 17 randomized and nonrandomized studies were synthesized, with findings suggesting that rFVIIa was more efficacious compared with aPCC in treating acute joint bleeding episodes.[18] However, the aPCC arm included 2 studies on Autoplex T®‡ (now discontinued), which was different from Feiba in terms of composition and manufacturing process. The main components of Feiba include activated Factor X and prothrombin,[19] whereas Factors IX and VII were the putative active hemostatic proteases in Autoplex T.[20] Therefore, the dosing and clinical outcomes of these 2 agents are not comparable. These differences might have contributed to the variations in clinical outcomes compared with rFVIIa. In addition, the nontransparent Bayesian model used in that meta-analysis was not provided to the present authors on request, and it used specific unverified prior and conjugate distributional assumptions that may have affected the findings.

To summarize the research to date and to add to the current understanding of the efficacy of bypassing agents in the treatment of joint bleeds in hemophiliac patients with inhibitors, a systematic review of data from previously published clinical studies was carried out using a classic meta-analytic approach. The efficacy of aPCC and rFVIIa 90 or 270 μg/kg were compared, and the role of study characteristics as covariates was investigated in a fully transparent pooled meta-analysis of data from previously published clinical studies.

METHODS

Search Strategy and Data Extraction

A systematic search of the published literature on clinical studies that have compared the efficacy of aPCC and rFVIIa in the treatment of acute joint bleeds in patients with hemophilia A or B and inhibitors was

‡Trademark of Nabi, Inc., Boca Raton, Florida.