Transfusion and Apheresis Science xxx (xxxx) xxx–xxx

Contents lists available at ScienceDirect

Transfusion and Apheresis Science

journal homepage: www.elsevier.com/locate/transci

Treatment and prevention of bleeding in congenital hemophilia A patients with inhibitors

Jerome M. Teitel

Division of Hematology and Oncology, St. Michael's Hospital, Toronto, and Department of Medicine, University of Toronto, Canada

ARTICLE INFO

Keywords:
Hemophilia A
Factor VIII inhibitor
Inhibitor by passing activity
Activated prothrombin concentrate
Recombinant activated factor VII
Factor VIII
Novel agents
TFPI antagonists
ATIII antagonist
Concizumab
Emicizumab
Alpha 1 antitrypsin

ABSTRACT

The treatment of bleeding in hemophilia A patients with persistent inhibitory antibodies to factor VIII is problematic. The current standard hemostatic agents for inhibitor patients are recombinant activated factor VII (rFVIIa) and activated prothrombin complex concentrate (APCC). These "inhibitor bypassing agents" are less reliably effective than are replacement therapies for patients without inhibitors, and there are no validated laboratory assays to monitor their efficacy. Furthermore, only single rFVIIa and APCC products are available worldwide, and their use can be complicated, albeit rarely, by thrombotic events. For all these reasons, new approaches to treat bleeding in inhibitor patients are eagerly awaited. These new approaches include replacement therapy with porcine factor VIII concentrate (currently approved for use in acquired hemophilia patients), bispecific antibodies to simulate the biologic function of factor VIII (already in use in some jurisdictions), pegylated forms of activated factor VII, and strategies targeting the natural anticoagulants TFPI and antithrombin, which create a hypercoagulable phenotype to counterbalance the hypocoagulability imposed by hemophilia.

1. Historical background

Inhibitor antibodies to factor VIII render hemophilia A patients resistant or refractory to treatment with replacement therapy. The traditional approach to achieve hemostasis in such patients is to use agents that promote thrombin generation without the need for the intact intrinsic factor Xase reaction, which is the target of the inhibitor. The earliest approach to "inhibitor bypassing therapy" was suggested by an observation by Breen and Tullis in 1969. In exploring the hemostatic effect of the recently introduced prothrombin complex concentrates (PCC) for deficiencies of factor IX and other vitamin K dependent proteins, these authors included a patient with hemophilia A with scrotal bleeding after a hydrocele repair [1]. The patient (whose inhibitor status was not described) had a prompt clinical response, which the authors attributed to stimulation of contact activation, based on shortening of the silicone coagulation time. Fekete and colleagues reasoned that activated coagulation enzymes were responsible for this patient's clinical response, and that it might be similarly effective in patients with inhibitors. In 1972 they reported on the efficacy of an activated PCC preparation for bleeding in patients with factor VIII inhibitors [2]. As activated PCC were not standardized, were expensive, and were in short supply, the hemostatic efficacy of non-activated PCC in factor VIII (FVIII) inhibitor patients was assessed in several studies [3–5], although in some of these reports both activated and non-activated PCC were used. A randomized double-blinded controlled trial confirmed the superiority of two PCC preparations over albumin [6]. Interest in the activated form of PCC persisted, stimulated by publications in prominent journals [7,8]. Ultimately a Dutch group performed a randomized double-blind trial comparing the efficacy of activated and non-activated PCC in sequential bleeds at the same intra-articular and intramuscular sites [9]. This study showed greater perceived efficacy and improved mobility of the involved joint in response to activated PCC. In contrast a subsequent double-blinded randomized trial by Lusher and colleagues comparing different preparations of both PCC and activated PCC (given in two dosages) showed no difference in subjective or objective (joint range of motion) responses [10].

The mechanism of action of these concentrates in FVIII inhibitor patients was a matter of debate, but the demonstration by Seligsohn and colleagues of activated factor VII (FVIIa) in both forms of PCC but in higher concentrations in activated preparations [11] led to interest in this enzyme as an inhibitor bypassing strategy. Hedner and Kisiel reported dramatic responses to purified human FVIIa in two children with inhibitors, one with an intramuscular bleed and one with a hemarthrosis and bleeding from a tooth socket [12]. This was followed only a few years later by the cloning and expression of recombinant human FVII [13], and the demonstration of the efficacy of the active enzyme form of the recombinant protein in hemophilic dogs and in human inhibitor patients [14–16]. Recombinant FVIIa and APCC both continue to be standard treatments for bleeding in inhibitor patients.

E-mail address: teitelj@smh.ca.

https://doi.org/10.1016/j.transci.2018.07.011

2. Recombinant factor VIIa (rFVIIa)

There is currently only a single rFVIIa treatment product available. The therapeutic window is wide, with individual doses ranging between 90 and 300 mcg/Kg. The standard dose of 90 mcg/Kg achieves plasma factor VII activity levels of 17–24 IU/ml [17]. Pharmacokinetic (PK) analysis of factor VII activity established median estimates for terminal half-life of 2.89 h in non-bleeding subjects and 2.30 h in bleeding patients [18]. Clearance is accelerated in children, in whom the half-life has been estimated at 1.32 h [19]. The treatment interval in acute bleeding events is therefore typically 2–3 hours. Using this regimen, the effectiveness of home infusion (one to three infusions at 3 h intervals) was 92% [20]. Analysis of over 2000 treated bleeding events recorded on a database maintained by the Hemostasis and Thrombosis Research Society (HTRS) showed bleeding cessation rates of 89% for spontaneous bleeds and 93% for traumatic bleeds [21]. The median number of doses was 3–4 depending on the bleeding site, with individual doses approximately 120 mcg/Kg. Higher doses, up to 300 mcg/Kg, have been used with good efficacy and safety [22]. Registry data revealed a dose-response relationship, with effective hemostasis secured at a rate of 84% for rFVIIa doses up to 200 mcg/Kg, and 97% for doses above this level [23]. The concurrent use of antifibrinolytic agents is considered safe with rFVIIa, and is widely practiced.

rFVIIa has also been used prophylactically to prevent, rather than treat, bleeding in inhibitor patients. Konkle and colleagues randomized twenty-two patients to two different daily doses of rFVIIa (90 and 270 mcg/Kg) for 3 months [24]. Both dose regimens resulted in reduced bleeding rates (45% and 59% respectively), with much of the benefit carried over into the 3-month post-prophylaxis interval. However, while on the two prophylaxis regimens, patients reported 2.2 and 3.0 bleeding events per month, rates considerably higher than observed in trials of prophylaxis with replacement therapy in patients without inhibitors [25,26].

Many clinicians have been understandably reluctant to recommend elective surgery in inhibitor patients, because of the incomplete and unpredictable hemostatic efficacy of bypassing agents, and the inability to provide laboratory monitoring that correlates with efficacy. Nevertheless, many surgical procedures, both minor and major, have been performed in patients treated with rFVIIa. In a prospective trial comparing two doses of rFVIIa in surgery (35 and 90 mcg/Kg) 28 of 29 patients achieved intra-operative hemostasis [27]. The efficacy rate for major surgery as judged at day 5 was 83% for the 90 mcg/Kg dose and only 40% for the 35 mcg/Kg dose. A review of the surgical and interventional experience with rFVIIa published in 2011 included registry databases and the available literature [28]. Three hundred ninety-five procedures were identified, in which rFVIIa was administered by bolus injection or by continuous infusion. The effectiveness was comparable across data sources, with an overall efficacy rate of 84%. The incidence of thrombotic events was very low (0.4% of patients and 0.025% of procedures). A more recent publication reviewed the results of case series of elective orthopedic surgery carried out under cover of rFVIIa over 3 decades. The report (which was supported by the manufacturer of rFVIIa) identified 380 cases, in which efficacy ranged between 67 and 100%, with no reports suggesting an increased incidence of thrombotic adverse events [29]. A six-person expert consensus panel has recommended a protocol for surgery with rFVIIa. They recommended a preoperative dose of 120–180 mcg/Kg, followed by 90 mcg/Kg every 2 h for 48 h, then further extending the treatment interval to 3 and 4 h (48 and 72 h later) if hemostasis is effective [30]. The recommended duration of treatment was 10–12 days, and the concomitant administration of tranexamic acid was recommended unless it was contraindicated.

The potential utility of managing surgery and the postoperative period with continuous infusion of rFVIIa was addressed in a prospective multi-institution study [31]. Nine patients undergoing major orthopedic surgery (8 arthroplasties and 1 amputation) were given a bolus injection of rFVIIa (90 mcg/Kg) pre-operatively, and concurrently started on an infusion at 50 mcg/Kg per hour. They were able to maintain FVII coagulant activity above 30 IU/ml, which was their therapeutic target. Although all patients were judged to have a good outcome, 6 patients had postoperative bleeds, 5 of which were operative site hemarthroses requiring additional bolus rFVIIa dosing. Continuous infusion of rFVIIa has not become a widely used method of administration.

The risk of thromboembolic adverse events (TAE) has been of great concern with the use of inhibitor bypassing agents. A review conducted through the pharmacovigilance program of the US Food and Drug Administration enumerated TAE reported for the 38 month period beginning in April 1999, when rFVIIa was introduced in the USA. The number of reported TAE associated with rFVIIa use was 67 (one of which was fatal), giving an estimated incidence rate of 24.6 per 10 000 infusions [32]. A review of events reported in a later time period, 2003–2006, including clinical trials and both spontaneous and solicited reports, yielded a lower estimated TAE incidence of 3.75 per 10 000 infusions. The absolute number of TAE was 30, of which 5 were fatal [33].

3. Activated PCC (APCC)

The effectiveness of APCC in treating bleeding in inhibitor patients and its superiority compared to PCC was established over 30 years ago [9]. An observational study by Hilgartner and colleagues reported a 93% hemostatic efficacy rate in 165 bleeding episodes in 46 FVIII and FIX inhibitor patients, 78% of them responding to one or two infusions [34]. There is currently only one commercially available APCC product, which has been in continuous clinical use since 1977.

APCC has been used prophylactically in inhibitor patients, both during immune tolerance induction regimens, as in the original “Bonn protocol” [35,36] and as long term therapy in patients with refractory inhibitors. The latter scenario was addressed in the “ProFEIBA Study” [37]. Twenty-six evaluable patients were randomized in a cross-over design to compare APCC given on-demand versus prophylactically in a dose of 85 units/Kg three times weekly, each for 6 months. The prophylactic regimen reduced the rate of bleeding by 62% compared to on-demand use, although the bleed event rate of 5.0 over 6 months was considerably higher than is typically seen during prophylaxis with replacement therapy in patients without inhibitors. No TAE occurred in this study. In another study addressing the value of prophylaxis, 17 refractory inhibitor patients were randomized to prophylactic infusions of APCC on alternate days in a dose of 85 units/Kg, and 19 were randomized to on-demand treatment [38]. The study duration was one year. Patients on the prophylaxis arm experienced 72.5% fewer bleeding events than those treated on-demand. As in the ProFEIBA study, the median annualized bleeding rate of 8.1 in the APCC prophylaxis arm would be considered unacceptably high in patients without inhibitors.

APCC has been widely used to prevent surgical bleeding in inhibitor patients, although most reports are of retrospective cohort studies. A Norwegian group reported 14 minor and 5 major surgeries in 8 patients, using an APCC regimen of 100 U/Kg as a preoperative bolus dose followed by 200 U/Kg/d given in 3 divided doses. Two patients who had major surgery became substantially anemic postoperatively, in one case sufficiently to require red cell transfusion [39]. One patient had a serious TAE, a non-ST elevation myocardial infarction on postoperative day 3. This patient was 69 years of age, wheelchair-bound and a former smoker. The decision was made to continue treatment with APCC, and there was no progression of his infarction. A French group published their retrospective experience with APCC to cover surgery between the years 1989 and 2004 [40]. Twelve procedures, ten of them classified as major, were performed in 7 patients, using a regimen of 70 U/Kg every 8 h. Blood loss and transfusion requirements (needed in 8 patients) were judged “as expected” for patients without inhibitors. A group of