ORIGINAL ARTICLE

Use of Haemate® P as immune tolerance induction in patients with severe haemophilia A who failed previous induction attempts: a multicentre observational study

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Summary. Immune tolerance induction (ITI) can eliminate factor VIII (FVIII) inhibitory antibodies that appear during FVIII replacement therapy. If first-line ITI fails, switching to a different FVIII concentrate, especially one containing von Willebrand factor (VWF), has been advocated. The objective of the study was to assess the efficacy and safety of Haemate® P, a plasma-derived FVIII concentrate containing high levels of VWF, as ITI in severe haemophilia A patients who had failed at least one prior ITI attempt with a different FVIII concentrate. In this multicentre, observational study, Haemate® P was administered at a starting dose of 83–308 IU kg⁻¹ day⁻¹ (1500–6000 IU day⁻¹). Efficacy was assessed by standard criteria (e.g. Bethesda titre, FVIII recovery and half-life), and bleeding characteristics. Nine patients from six haemophilia centres were treated with Haemate® P after failing one (n = 2), two (n = 5) or three (n = 2) prior ITI courses. The median time from inhibitor detection to Haemate® P treatment was 5.4 years. The median Haemate® P dose was 134 IU kg⁻¹, and the median treatment duration 32 months. During median of 47 months of follow-up, complete response, partial response and treatment failure were observed in one, three and five patients respectively. Five patients experienced seven adverse events (AEs), including two serious AEs (sepsis). Haemate® P was discontinued due to an AE in one patient with a partial response. Haemate® P salvage ITI resulted in complete or partial tolerization in four of nine patients (44%) who had failed previous ITI attempts using different FVIII concentrates.

Keywords: factor VIII, haemophilia A, immune tolerance induction, inhibitors, von Willebrand Factor

Introduction

Use of factor VIII (FVIII) concentrates to treat and prevent bleeding episodes in patients with haemophilia A triggers the appearance of anti-FVIII antibodies (inhibitors) in 15–30% of cases, representing the most serious complication of FVIII replacement therapy [1–3]. Inhibitor eradication by immune tolerance induction (ITI) can be achieved in approximately 70% of patients. The time to tolerance varies from 1 month to 2 years, and can reach up to 33 months in some cases [3–10]. The optimal first-line ITI protocol has not been defined, and proposed methods vary with regard to dose (from 25 IU kg⁻¹ three times weekly to 100 IU kg⁻¹ twice daily) [4,7], treatment duration (0.5–2 years) [5,11] and method of discontinuation once ITI is achieved (abrupt discontinuation versus gradual decrease) [4–6,8,12]. The optimal type of FVIII concentrate also remains controversial [11,13]: some authors have suggested that intermediate-purity FVIII concentrates, which contain higher amounts of von Willebrand factor (VWF), may facilitate immune tolerance [3,13] and are more effective [14], whereas others have reported comparable success rates with recombinant and high-purity, plasma-derived FVIII concentrates [15,16].

First-line ITI fails in approximately 20–40% of patients [reviewed in 17]. Switching to a different
FVIII concentrate has been proposed for managing these patients. The only FVIII concentrate currently approved for ITI in France is Factane® (LFB Biomedicaments, Les Ulis, France), a high-purity, plasma-derived product containing VWF. Haemate® P (CSL Behring, Paris, France) is a plasma-derived FVIII concentrate that contains high levels of VWF (1000 IU FVIII:C and 2400 IU VWF:RCo) and has been successfully used as ITI in children [6,17–20] and adults [18,21–24]. In France, patients who fail first-line ITI may receive Haemate® P via a temporary authorization procedure. The objective of this study was to describe the efficacy and safety of Haemate® P when used as ITI in patients with severe haemophilia A who were resistant to at least one previous course of ITI using a different FVIII replacement concentrate.

Patients, materials and methods

This multicentre, retrospective, open-label, uncontrolled, observational study included patients from six haemophilia centres in France (Caen, Kremlin-Bicêtre, Lyon, Montpellier, Paris, Tours). As per local law, the study protocol was submitted to CNIL (Commission Nationale Informatique et Liberté) and a verbal consent was required. All patients had severe haemophilia A (FVIII <1%) and anti-FVIII inhibitors and had undergone at least one prior ITI therapy. Patients received Haemate® P by intravenous infusion. The treating physician determined the starting dose.

Data were collected from March 2005 to June 2009, and patients were followed up until January 2011. A case report form was used to collect the following data: (i) date of visit; (ii) date of birth, date of haemophilia diagnosis, baseline FVIII level and F8 gene mutation; (iii) date of inhibitor detection, cumulative exposure days at inhibitor detection, inhibitor titre at detection and maximum titre recorded; (iv) history of ITI prior to Haemate® P (product name, dose, regimen, start/end dates and reason for change); (v) bleeding events during previous ITI; (vi) use of bypassing agents during treatment with Haemate® P; (vii) evolution of inhibitor titres; and (viii) modalities of treatment with Haemate® P and adverse events.

Outcomes following ITI with Haemate® P were assessed using the following standard criteria [11]:

1. Success/complete response (CR): inhibitor titre <0.6 Bethesda units [BU], FVIII recovery ≥66% and FVIII half-life ≥6 h
2. Biological partial response (BPR): inhibitor titre ≤5 BU or FVIII recovery <66% or FVIII half-life ≤6 h
3. Clinical partial response (CPR): inhibitor titres >5 BU, but marked reduction in spontaneous bleeding and improved bleeding pattern, possibly associated with clear improvement in quality of life
4. Failure: persistence of inhibitor titre >5 BU for more than 33 months and no change in spontaneous bleeding events.

The efficacy population consisted of patients with documented ITI outcome assessment and postbaseline inhibitor titres. The safety population consisted of patients who received at least one dose of Haemate® P.

Results

Nine patients with severe haemophilia A (FVIII <1%) and a median age of 8.5 years (range 3.5–46 years) were included. Patient characteristics, including F8 gene mutation, are shown in Table 1. At the time of inhibitor detection, one patient was receiving cryoprecipitate and the remaining eight patients were receiving plasma-derived (n = 1) or recombinant (n = 7) FVIII concentrates. The duration of exposure was known for seven patients and ranged from 4 to 27 days. Inhibitor titres at the time of detection were known for eight patients: three had inhibitor titres <10 BU and five had titres >10 BU. All patients were identified as high responders, and the median peak historical inhibitor titre was 200 BU (mean 754.6 BU; range 55–3840 BU).

Before receiving Haemate® P, patients had received one (n = 2), two (n = 5) or three (n = 2) courses of unsuccessful ITI. First-line ITI consisted of Kogenate® (Bayer Santé, Loos, France) (n = 2), Recombinate® (Baxter, Maurepas, France) (n = 2), Refacto® (Pfizer, Paris, France) (n = 2), Factane® (LFB, Les Ulis, France), Advate® (Baxter, Maurepas, France) or Helixate® (CSL Behring, Paris, France) (n = 1 each). Seven patients were offered a second-line ITI consisting of Factane® (n = 6) or Advate® (n = 1). Two patients received third-line ITI consisting of either Factane® or Recombinate®. Thus, Haemate® P was administered as second- (n = 2), third- (n = 5) or fourth-line therapy (n = 2).

The median time from inhibitor detection to the start of ITI therapy with Haemate® P was 5.4 years (range 1.5–27.4 years). The median inhibitor titre before starting Haemate® P was 20.6 BU (range 6.3–160 BU). The median starting dose of Haemate® P was 134 IU kg⁻¹ per injection (range 83–308 IU kg⁻¹) and the median number of injections per week was 14 (range 3.5–14). The median duration of ITI therapy with Haemate® P was 32 months (range 11–70 months) (Table 1). NovoSeven® (Novo Nordisk, Puteaux, France) and FEIBA® (Baxter, Maurepas, France) were administered as needed for treatment or prevention of breakthrough bleeding.

The median duration of follow-up after study completion was 47 months (range, 29–70 months). Response outcomes during follow-up were as follows:

1. Success/CR occurred in one patient (Patient 6). This patient had an immediate and dramatic reduction in inhibitor titre (from 160 BU to
Table 1. Patient characteristics and outcomes.

<table>
<thead>
<tr>
<th>Patient</th>
<th>Age at study start (years)</th>
<th>F8 gene mutation (HGVS nomenclature)</th>
<th>Treatment at time of inhibitor detection</th>
<th>CED at inhibitor detection (days)</th>
<th>Inhibitor titre at the time of detection (BU mL⁻¹)</th>
<th>Historical peak inhibitor titre (BU mL⁻¹)</th>
<th>Number of prior ITI courses (treatment given)</th>
<th>Time from inhibitor detection to start of Haemate® P (years)</th>
<th>Inhibitor titre at start of Haemate® P (BU mL⁻¹)</th>
<th>Duration of ITI with Haemate® P (months)</th>
<th>Last known inhibitor titre (BU mL⁻¹)</th>
<th>Outcome*</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>46</td>
<td>Deletion of exons 6–14</td>
<td>PD (cryoprecipitate)</td>
<td>Unknown</td>
<td>4</td>
<td>128</td>
<td>3 (Recombinate, Factane, Recombinate)</td>
<td>27.4</td>
<td>20.6</td>
<td>70.0</td>
<td>4.0 (November 2008)</td>
<td>BPR + CPR; ITI continues</td>
</tr>
<tr>
<td>2</td>
<td>6</td>
<td>Exon 14 deletion</td>
<td>R (Kogenate)</td>
<td>4</td>
<td>14 Nij</td>
<td>3840</td>
<td>2 (Helixate, Factane)</td>
<td>5.4</td>
<td>27.0</td>
<td>42.0</td>
<td>22.0 (December 2008)</td>
<td>Failure; ITI stopped</td>
</tr>
<tr>
<td>3</td>
<td>9</td>
<td>c.1760C&gt;A (p.Ser587Stop)</td>
<td>R (Refacto)</td>
<td>7</td>
<td>55</td>
<td>55</td>
<td>3 (Recombinate, Advate, Factane)</td>
<td>8.9</td>
<td>27.0</td>
<td>11.0</td>
<td>19.0 (March 2009)</td>
<td>Failure; ITI stopped</td>
</tr>
<tr>
<td>4</td>
<td>4.5</td>
<td>c.3406delT (p.Ser1136LeufsX2)</td>
<td>R (Advate)</td>
<td>17</td>
<td>6</td>
<td>313</td>
<td>2 (Advate, Factane)</td>
<td>3.4</td>
<td>11.2</td>
<td>26.0</td>
<td>26.0 (March 2009)</td>
<td>Failure; ITI stopped</td>
</tr>
<tr>
<td>5</td>
<td>3.5</td>
<td>Intron 1 inversion</td>
<td>R (Recombinate)</td>
<td>9</td>
<td>65</td>
<td>65</td>
<td>1 (Recombinate)</td>
<td>2.8</td>
<td>6.3</td>
<td>45.0</td>
<td>0.7 (February 2009)</td>
<td>BPR + CPR; ITI continues</td>
</tr>
<tr>
<td>6</td>
<td>15</td>
<td>c.1804C&gt;T (p.Arg602Xstop)</td>
<td>PD (Factane)</td>
<td>Unknown</td>
<td>Unknown</td>
<td>190</td>
<td>1 (Factane)</td>
<td>7.8</td>
<td>160.0</td>
<td>&gt;57</td>
<td>0.0 (November 2006)</td>
<td>CR; ITI continues</td>
</tr>
<tr>
<td>7</td>
<td>8.5</td>
<td>c.3833delA (p.Asn1278IlefsX30)</td>
<td>R (Kogenate)</td>
<td>27</td>
<td>41</td>
<td>200</td>
<td>2 (Kogenate, Factane)</td>
<td>1.5</td>
<td>11.5</td>
<td>32.0</td>
<td>0.4 (June 2008)</td>
<td>BPR + CPR; ITI stopped due to AE</td>
</tr>
<tr>
<td>8</td>
<td>4.9</td>
<td>Intron 22 inversion</td>
<td>R (Kogenate)</td>
<td>18</td>
<td>2.3</td>
<td>600</td>
<td>2 (Kogenate, Factane)</td>
<td>3.4</td>
<td>71.0</td>
<td>26.0</td>
<td>13.0 (April 2009)</td>
<td>Failure; ITI stopped</td>
</tr>
<tr>
<td>9</td>
<td>6.9</td>
<td>Intron 22 inversion</td>
<td>R (Refacto)</td>
<td>15</td>
<td>36</td>
<td>1400</td>
<td>2 (Recombinate, Advate, Factane)</td>
<td>5.6</td>
<td>52.0</td>
<td>21.0</td>
<td>7.0 (June 2008)</td>
<td>Failure; ITI stopped</td>
</tr>
</tbody>
</table>

AE, adverse event; BPR, biological partial response; BU, Bethesda units; CED, cumulative exposure days; CPR, clinical partial response; CR, complete response; ITI, immune tolerance induction; Nij, Nijmegen; PD, plasma-derived; R, recombinant.

*As of June 2009.
2.4 BU) within the first month of receiving prophylactic treatment with Haemate® P (45 IU kg⁻¹ every second day) (Fig. 1).

2. Partial response occurred in three patients (Patients 1, 5 and 7) (Fig. 2). All three patients achieved both a BPR and CPR. Patient 1 had a dramatic reduction in bleeding episodes and consumption of bypassing agents.

3. Failure was documented in five patients (Patients 2, 3, 4, 8 and 9) and Haemate® P was discontinued. Patient 2 initially achieved a CPR associated with reduced bleeding episodes and consumption of bypassing agents, but treatment failure was later reported (increase in inhibitor titre after 42 months of ITI treatment with Haemate® P).

Five patients experienced seven adverse events (AEs): four of these were deemed possibly related to Haemate® P by the investigator (gastroenteritis; endocarditis; nausea, dizziness and vomiting; and port sepsis with glomerulonephritis and endocarditis), and one AE was deemed likely related to study treatment (trembling in extremities and tongue during infusion). Other AEs included cranial trauma; cough without fever; gastroenteritis; trembling in extremities and tongue during infusion; endocarditis; nausea, dizziness and vomiting; and port sepsis with glomerulonephritis and endocarditis. Two patients experienced serious AEs requiring hospitalization: one patient (Patient 8) had endocarditis lasting 51 days; the other (Patient 9) had port sepsis with glomerulonephritis and endocarditis, lasting 70 days. Endocarditis was considered related (n = 1) or likely related (n = 1) to port sepsis. Resolution of all AEs was observed during the study period. No thromboembolic events were reported. One patient (Patient 7) discontinued Haemate® P due to an AE possibly related to treatment (tremor in extremities and tongue during infusion), and continued ITI with another treatment.

Fig. 1. Inhibitor titre variations in one patient with successful response to immune tolerance induction. BU, Bethesda units.

Fig. 2. Inhibitor titre variations in three patients with a biological and/or clinical partial response to immune tolerance induction. BU, Bethesda units.
Discussion

This is the first multicentre evaluation of the use of Haemate® P during ITI in France. We chose a retrospective study design using a case report form because the number of haemophilia A patients in France who received ITI with Haemate® P was low. The study design also met requirements established by the French Health Products Safety Agency (AFSSAPS), allowing for careful follow-up, reliable data collection and assessment with internationally accepted outcome measures.

Response (complete or partial response) was observed in four of the nine patients. This success rate is particularly promising given that all patients had failed prior ITI attempts using recombinant or plasma-derived FVIII concentrates, and therefore could be considered as poor prognostic subjects. Patients had received a median of two prior ITI courses, the median time from inhibitor detection to start of Haemate® P was relatively long (5.4 years), and only one patient had an inhibitor titre <10 BU at the start of Haemate® P treatment. Given the low probability of responding to further ITI attempts in this patient population, the observed responses to Haemate® P are encouraging.

Based on the type and frequency of reported AEs, there was no indication that ITI with Haemate® P was associated with a particular type of AE. Eight patients had a central venous catheter, and two developed port-related sepsis and subsequent endocarditis. Infections are the main risk associated with these devices, highlighting the need to minimize the duration of their use. High-dose ITI protocols, however, may require central venous access.

Starting doses of Haemate® P in our study ranged from 1500 to 6000 IU day⁻¹ (83–308 IU kg⁻¹). There is no consensus in the literature regarding the optimal starting dose of ITI. Some have reported that high doses are more effective, especially in patients with inhibitor titres >10 BU [5], but no consistent dose–response relationship was found in ITI registry data [8,12,25,26]. Low-dose regimens have also been shown to produce high success rates [7]. In a randomized study comparing low-dose ITI (50 IU kg⁻¹ x 3 weekly) with high-dose ITI (200 IU kg⁻¹ daily), high-dose ITI was associated with a significantly shorter time to inhibitor eradication and FVIII recovery normalisation, but success rates were comparable in both groups [27]. Additional studies are needed to determine the optimal ITI starting dose.

Our complete/partial success rate (4/9 patients; 44%) is lower than the 80% (8/10 patients) reported by Kreuz et al. [28] using Haemate® P as first line, but higher than the lack of success (0/4 patients) reported by Greninger et al. [13] using a different VWF-containing FVIII concentrate (Alphanate®, Grifols, Barcelona, Spain). Other groups have reported comparable rates of complete and partial responses [3,28].

Multiple factors influence ITI success [5,8,12]; the most robust predictive factor is inhibitor titre <10 BU at ITI initiation [1,5,8,25]. A shorter time from inhibitor detection to the start of ITI was found to predict success in some studies [5,6], but not in others [7,8,25]. Prognostic factors for salvage ITI are less well defined, but low inhibitor titre (<10 BU) and early switching (within 6 months) from ITI with recombinant or high-purity, plasma-derived FVIII to VWF-containing FVIII concentrates have been reported [3]. The latter is supported by data from preclinical [29–36] and clinical studies [3,10,18,37–39], which indicate that switching from a recombinant or high-purity, plasma-derived FVIII concentrate to a VWF-containing FVIII concentrate may be beneficial.

Whether VWF content influences ITI success has not been definitively established. In FVIII-knockout mice, VWF content was shown to influence the antigenicity of the FVIII concentrate: products containing little or no VWF were more likely to elicit anti-FVIII inhibitors [35]. Binding of VWF to FVIII may protect FVIII from inhibitors with A2 and light-chain subunit specificity [13,31–36], and some evidence suggests that ITI success may depend in part on inhibitor epitope specificity [13]. Although this preliminary evidence is compelling, the superiority of VWF-containing FVIII concentrates for ITI remains to be demonstrated.

In conclusion, ITI with Haemate® P led to complete or partial immune tolerance in four of nine patients with severe haemophilia A who were unlikely to achieve tolerance given their medical history. Few serious AEs were reported in this series, and according to commonly accepted international criteria, Haemate® P appears to be a safe and effective choice for ITI, particularly in patients who have failed previous ITI attempts.

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Author contributions

CN coordinated the research. CN, CR, RN, RdO, YG and ABD were study investigators (enrolled patients) and revised the manuscript. CN analysed the data and wrote the manuscript.

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Disclosures

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