Haemophilia
The Official Journal of the World Federation of Hemophilia,
European Association for Haemophilia and Allied Disorders and
the Hemostasis & Thrombosis Research Society

Haemophilia (2015), **21**, e122–e150

LETTERS TO THE EDITORS

Prospective, observational study of plasma-derived factor VIII/von Willebrand factor in immune tolerance induction: the PRISM registry

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Haemophilia A (factor VIII [FVIII] deficiency) is a rare bleeding disorder and the most common type of haemophilia. Although largely inherited, approximately 30% of haemophilia A cases are due to spontaneous gene mutations in patients with no family history of haemophilia. Several recombinant and plasma-derived factor VIII (pdFVIII) products are available to prevent or treat bleeding caused by haemophilia and reduce the risk of long-term complications.

The most serious treatment complication for patients with haemophilia A is the development of inhibitory IgG antibodies to FVIII [1–3]. Inhibitors result in rapid clearance of infused FVIII and marked reduction or absence of efficacy. Recombinant activated factor VII (rFVIIa) and FVIII inhibitor bypassing activity are two agents used to treat acute bleeding in patients with inhibitors [2]. However, inhibitor eradication is the goal of long-term management. Immune tolerance induction (ITI) therapy using frequent administration of high FVIII doses, sometimes in combination with immunomodulatory or immunosuppressive drugs, is the only strategy that has been shown to achieve antigen-specific tolerance [1,3].

Other than the International Immune Tolerance Study [1], few prospective studies have been conducted that describe how patients with haemophilia A respond to ITI therapy. Published studies of the efficacy and safety of primary and rescue ITI using pdFVIII/von Willebrand Factor (VWF) concentrates are largely retrospective [3–6]. Additionally, there is little retrospective and no prospective, long-term follow-up of immune tolerance, quality of life (QOL) on ITI and adherence to ITI regimen. Prospective studies investigating the efficacy and safety of ITI therapy in patients with haemophilia include the RITS-FITNHES Study [7], the International Immune Tolerance Study [1] and the REScue Immunotolerance Study (RESIST) [8].

The RITS-FITNHES Study investigated the effectiveness of ITI using pdVWF/FVIII complex concentrate in 17 patients with severe or moderate haemophilia A and inhibitors who were at high risk for failure [7]. Nine (53%) patients had complete success (inhibitor titre <0.5 BU) after 4–30 months of treatment, seven patients had partial success (inhibitor titre 1.1–2.8 BU), while one patient withdrew ITI after 12 months when inhibitor titre was 70 BU.

The International Immune Tolerance Study, a multicentre, prospective, randomized study, compared high-dose (200 IU kg^{-1} day^{-1}) and low-dose (50 IU kg^{-1} three times per week) FVIII regimens in 'good risk' subjects with severe haemophilia A and high-titre inhibitors [1]. Results from the study showed that 66 (57%) of the 115 subjects reached a study endpoint with 69.7% of them achieving a complete success, 4.5% achieving a partial success and 25.8% failing to achieve any success (no difference found in the success rate between the two treatment arms). Although there was no overall difference in the median time to achieve success between the two groups, the median times from start of ITI to first negative titre and from negative titre to first normal recovery were shorter in the high-dose group than in the low-dose group.

RESIST originally comprised two ongoing trials, complementing the International Immune Tolerance Study, to evaluate the use of VWF-containing FVIII products in ITI [8]. One trial, $RESIST_{exp}$ (Clinicaltrials.gov Identifier NCT01051076), was designed as a prospective, open-label study in which a high dose of FVIII/VWF (200 IU kg^{-1} daily) is used in patients with inhibitors who have failed a previous ITI attempt with a VWF-free FVIII concentrate (plasma-derived or recombinant). The second trial, $RESIST_{naïve}$ (Clinicaltrials.gov Identifier NCT01051544), was designed as a study of patients with inhibitors who are at high risk to fail ITI; patients were randomized to receive either

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Accepted after revision 28 October 2014

DOI: 10.1111/hae.12590

a VWF-containing FVIII concentrate (200 IU kg^{-1} daily) or a non-VWF-containing FVIII concentrate (plasma-derived or recombinant). $RESIST_{naïve}$ has stopped enrolling new patients as of April 2013; $RESIST_{exp}$ has stopped enrolling new patients as of June 2014. These studies will not be reporting outcomes as originally envisioned.

We are conducting the ***PR***ospect***I***ve Observational ***S***tudy of Plas***M***a-derived FVIII/VWF in Immune Tolerance Induction (PRISM) Registry in patients with haemophilia A with inhibitors who are undergoing ITI using Alphanate®(antihaemophilic factor VIII/VWF Complex [Human]; Grifols Biologicals Inc., Los Angeles, CA, USA) with a primary or rescue (salvage) ITI protocol. Alphanate is indicated for the control and prevention of bleeding in patients with haemophilia A. This prospective registry follows work completed by Kurth and colleagues [3], who performed a retrospective medical record review of patients with haemophilia A who received pdFVIII/VWF in either primary or rescue ITI at 11 institutions in the United States. Given the limited information available on real-world outcomes, including long-term (>12 months) sustainability of response [9], in patients undergoing ITI, the PRISM Registry will assess the immediate and long-term patient response to ITI therapy for up to 10 years.

The PRISM Registry is a multicentre, prospective, observational study of patients with congenital haemophilia A who are receiving treatment in the United States with Alphanate as either primary or rescue ITI. The primary objectives of this study are to assess patient response to ITI, assess patient ability to tolerate ITI treatment, estimate the treatment discontinuation rate and assess the frequency of targeted adverse events during ITI therapy. Secondary objectives of this study are to evaluate patient QOL before, during and upon successful completion of ITI; evaluate adherence to ITI treatment; assess bleeding rates before, during and after ITI treatment; and assess long-term maintenance of response to ITI [9]. It is anticipated that patients will be identified at approximately 20–30 haemophilia centres in the United States. Anticipated enrolment is approximately 100 patients (10 entered per year for 10 years) and is based on pragmatic consideration of the number of patients expected to enrol during the maximally feasible study duration rather than explicit statistical considerations.

Inclusion criteria are: a diagnosis of congenital haemophilia A with FVIII <2%; high responding inhibitor (titre ≥5 BU mL^{-1} recorded at any time) or if a low responding inhibitor (persistently <5 BU mL^{-1}), the patient is, in the investigator's judgment, a candidate for ITI or has already initiated ITI with Alphanate; have initiated treatment with Alphanate as either primary or rescue (salvage) ITI within the previous 6 months or the clinical decision has been made to initiate ITI treatment with Alphanate within the next 8 weeks if younger than 18 years, will be required to have a caregiver willing to participate and provide information for them; and as appropriate based on the patient age, provide signed consent or assent and/or permission of parent or legal guardian. Exclusion criteria are: patients with acquired FVIII deficiency.

Outcomes to be evaluated are ITI effectiveness; bleeding rates before, during and after ITI; adverse events; long-term response (>12 months) to ITI; patient QOL and patient adherence to ITI therapy. Primary outcome definitions follow international consensus guidelines [10] with additional provisional categories included (if needed, due to the observational nature of the study) (Table 1). Patients who meet the criteria for success or partial success will be followed quarterly for one additional year, and then annually for the duration of the study (up to 10 years) to determine maintenance of response. QOL and adherence data will be collected directly from patients or their caregivers at baseline, during ITI treatment and quarterly for 1 year after successful (or partially successful) ITI treatment.

Results will be summarized annually using descriptive statistical methods. In addition, associations between patient characteristics (classic treatment

Table 1. Primary outcome definitions

Complete Success*
Undetectable inhibitor level (<0.6 BU mL^{-1})
FVIII recovery ≥66% of predicted
FVIII half-life ≥6 h after a 72-h FVIII washout period
Absence of an anamnesis upon further FVIII exposure
Provisional Complete Success†
Criteria for inhibitor titre and absence of anamnesis for complete success are met, but either recovery or half-life information is not available
Partial Success (after 33 months of ITI)*
Reduction of inhibitor titre to <5 BU mL^{-1}
Clinical response to FVIII therapy
No increase in inhibitor titre exceeding 5 BU over a 6-month period of on-demand treatment or 12 months of prophylaxis and either:
FVIII recovery <66% of predicted or
FVIII half-life <6 h after a 72-h FVIII washout period
Provisional Partial Success†
Criteria for inhibitor level and absence of anamnesis for partial success are met, but either recovery or half-life data not available
Failure
Failure to fulfil criteria for complete or partial success within 33 months or
<20% reduction in the inhibitor titre for any 6-month period during ITI after the first 3 months of treatment
Indeterminate
Response to ITI therapy cannot be determined due to limited duration of follow-up or unavailability of required data

*Documentation of recovery and half-life are required before assignment to complete or partial success can be made.
†Provisional categories are provided to accommodate real-world clinical practice where recovery and half-life may be not always available.
BU, Bethesda Units; FVIII, factor VIII; ITI, immune tolerance induction.

success factors), treatment patterns (including stratification by dose and frequency) and inhibitor outcomes will be analysed at the end of the study and compared to published criteria and results.

The PRISM Registry is the first prospective, long-term registry of patients with haemophilia A with inhibitors receiving treatment in the United States with Alphanate as either primary or rescue ITI. While restricting this study to the use of Alphanate does limit the potential generalizability of results to other FVIII/VWF-containing concentrates, it will allow for clear determination of the association of one treatment with resulting patient outcomes. The registry will be unique in collecting prospective long-term (>12 months) ITI outcome data, assessing bleeding rates at different time points during ITI, evaluating QOL during ITI and appraising adherence and factors affecting it. The PRISM Registry will complement currently available data and provide important, prospective information to support the management of patients with haemophilia A who develop inhibitors. Site and patient enrolment for the PRISM Registry is now open.

Acknowledgements

The authors acknowledge the PRISM Advisory Committee: Dr Lou Aledort (Mount Sinai Hospital, New York, NY), Dr Peter Kouides (Rochester General Hospital, Rochester, NY), Dr Roshni Kulkarni (Michigan State University, East Lansing, MI), Dr Shannon Meeks (Emory University, Atlanta, GA), Dr Nadia Ewing (City of Hope, Duarte, CA) and Judith Kauffman (Children's Mercy Hospital and Clinics, Kansas City, MO). Dr Rebecca Kruse-Jarres is also a member of the PRISM Advisory Committee. Medical writing assistance was provided by Latoya M. Mitchell, PhD CMPP, of Grifols.

Disclosures

This study is sponsored by Grifols, which manufactures Alphanate® (antihaemophilic factor/von Willebrand factor complex [human]). RKJ has acted as a paid consultant to Baxter, Bayer, Grifols and Novo Nordisk. JS is an employee of Grifols. AG and JAK are employees of RTI Health Solutions.

Author Contributions

RKJ, AG, JS and JAK made substantial contributions to the clinical design and protocol of the PRISM Registry and wrote, revised and approved the paper.

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