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Title: rFVIIIFc for immune tolerance induction in patients with severe haemophilia A with inhibitors – a retrospective analysis

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Abstract (250/250 words)

Introduction

Immune tolerance induction (ITI) is the gold standard for eradication of Factor VIII inhibitors in severe haemophilia A; however, it usually requires treatment for extended periods with associated high burden on patients and healthcare resources.

Aim

Review outcomes of ITI with rFVIIIFc in patients with severe haemophilia A and high-titre inhibitors.

Methods

Multicentre retrospective chart review of severe haemophilia A patients treated with rFVIIIFc for ITI.

Results

Of 19 patients, seven were first-time ITI and 12 were rescue ITI.

Of seven first-time patients, six had at least one high-risk feature for failure. Four of 7 first-time patients were tolerized in a median of 7.8 months. The remaining three patients continue on rFVIIIFc ITI.

Of 12 rescue patients, seven initially achieved a negative Bethesda titre (≤0.6) in a median of 3.3 months, one had a decrease in Bethesda titre and continues on rFVIIIFc ITI and four have not demonstrated a decrease in Bethesda titre. Of these four, three continue on rFVIIIFc ITI and one switched to bypass therapy alone. Two initially responsive patients transitioned to other factors due to recurrence.

Sixteen of 19 patients remain or rFVIIIFc (prophylaxis or ITI). For those still undergoing ITI, longer follow-up is needed to determine final outcomes. No adverse events reported.

Conclusions

rFVIIIFc demonstrated rapid time to tolerization in high-risk first-time ITI patients. For rescue ITI, rFVIIIFc showed therapeutic benefit in some patients who previously failed ITI with other products. These findings highlight the need to further evaluate the use of rFVIIIFc for ITI.

3039/3000 WORDS

Introduction

Haemophilia A is a congenital disease caused by factor VIII (FVIII) deficiency and results in spontaneous and traumatic bleeding [1]. Recurrent bleeding leads to disability, affects quality of life, and is potentially life-threatening [2]. The standard treatment is intravenous FVIII concentrates administered prophylactically; however, episodic treatment is also used [3, 4]. Exposure to FVIII is associated with risk of inhibitor development, which renders replacement FVIII ineffective [4, 5]. The development of inhibitors remains a key challenge in the treatment of haemophilia A and occurs in 25% to 35% of severely deficient patients (FVIII level <1%) [6, 7]. In patients with high-titre inhibitors (HTI), >5 Bethesda units (BU), the standard of care is eradication of the inhibitor by immune tolerance induction (ITI). Although ITI regimens vary, most involve the regular administration of high doses of FVIII over months/years to tolerize the immune system so that FVIII can again be used prophylactically for haemostatic control. Bypassing agents (recombinant activated FVII [FVIIa] and activated prothrombin complex concentrates [aPCCs]) are used to treat bleeding until tolerization is achieved [8-10]. Results from previous studies reveal ITI success rates from 50% to 88% [8, 10-18]. In those who

achieve successful ITI, it takes approximately 1 to 2 years. For those who fail an initial course of ITI, rescue ITI is often tried, usually involving a change in factor type. The success rates for those who have previously failed ITI and are tried on rescue ITI is much lower, but data are lacking.

Historically, the purported risk factors for ITI failure include historical peak inhibitor >200 BU, inhibitor titre of ≥10 BU at ITI start, age ≥8 years at ITI start, >2 years between inhibitor diagnosis and ITI start, interruptions in ITI for longer than 2 weeks [13, 19, 20], and previous ITI failure [12, 13, 16, 21]. For the most part, the risk factors for ITI failure are based on registry data and have not been well confirmed through randomized studies. A retrospective analysis by Nakar et al. [17] showed that inhibitor titre ≥10 BU at ITI start may not be a poor risk factor if ITI is started early.

Given that treatment is not successful in a substantial number of patients who undergo ITI and that it may take significant time to achieve success at great risk, cost and inconvenience for patients, there is a major unmet need for agents that are associated with increased response rates in a shorter time [22]. Recombinant factor VIII Fc fusion protein (rFVIIIFc [Eloctate®, Bioverativ, Inc., Waltham, MA]) is the first extended half-life FVIII approved to treat haemophilia A [23-26]. There is limited experience for its use in ITI. A case series of three patients with haemophilia A using rFVIIIFc for ITI (in one case for rescue ITI) suggested a more rapid time to tolerization compared with conventional FVIII products [27]. This notion is supported by several preclinical studies showing that the Fc protein of rFVIIIFc has immunomodulatory properties [28-32]. Here we report findings associated with the use of rFVIIIFc for ITI in 19 patients via retrospective chart review.

Materials and Methods

A noninterventional retrospective chart review of ITI with rFVIIIFc in patients with severe haemophilia A and HTI (≥5 BU) was conducted across 10 sites in the United States and Canada between July 1, 2014, and June 1, 2017. Male patients of all ages with severe haemophilia A and HTI who had initiated treatment with rFVIIIFc for ITI, either as primary or rescue therapy, regardless of response, were included.

After institutional regulatory approval, de-identified clinical information was collected via an electronic survey. Patients treated for the first time with ITI were considered at high risk for ITI failure according to the criteria listed earlier [13, 19, 20]. Negative Bethesda titre was defined as

≤0.6 BU. Tolerization was defined as negative Bethesda titre, normal FVIII recovery (≥66%) and half-life (≥6 hours) [13]. The primary objective of this study was to report the clinical characteristics and outcomes of ITI using rFVIIIFc. Results are summarized using descriptive statistics; no inferential statistical analysis was conducted.

Results

Study population

Nineteen patients were identified. Of these, seven were receiving ITI for the first time and 12 were undergoing rescue ITI (**Tables 1** and **2**). Median age at initiation of rFVIIIFc ITI was 1.3 years (range: 0.8–4.3 years) for first-time ITI and 6.4 years (range: 1.6–12.6 years) for rescue ITI patients. Given their young ages, most patients had central venous access devices (CVADs). This included five of seven first-time ITI patients and 11 of 12 rescue ITI patients. Of first-time ITI patients, three were black, three were white, and one was Asian. For the rescue ITI patients, the majority were white (10/12), one was black, and one was "other" race.

First-time ITI patients had a median peak historical inhibitor (pre-ITI) titre of 151 BU (range: 11–1126 BU) and a median inhibitor titre at start of rFVIIIFc ITI of 52 BU (range: 3–1126 BU). At the start of ITI, six of seven first-time ITI patients had titres >10 BU; four of these six had titres >50 BU. The median time from inhibitor diagnosis to start of rFVIIIFc ITI was 4.4 weeks (range: 0–41 weeks).

For rescue ITI patients, the mean number of prior ITI courses with other FVIII products was 2.6 (range: 1–5) and the median time from inhibitor diagnosis to the start of rFVIIIFc ITI was 5.5 years (range: 0.8–12 years). These patients had a median peak historical inhibitor (pre-ITI) titre of 124 BU (range: 8–1024 BU) and a median inhibitor titre at start of rFVIIIFc ITI of 24.2 BU (range: 0.6–237 BU). FVIII genotypes for 18 of the 19 patients are shown in **Tables 1** and **2**.

First-time ITI patient outcomes

At the time of data collection, four of seven patients undergoing first-time ITI with rFVIIIFc (**Table 1**) were tolerized and had transitioned to rFVIIIFc prophylaxis. Three of these four patients achieved a negative Bethesda titre and normal FVIII recovery and half-life (≥6 hours); as such, they met the definition of tolerization at 5, 7, and 9 months. These patients were all on

a daily rFVIIIFc (85–200 IU/kg) ITI regimen. The fourth patient was considered tolerized by the treating physician at 14.8 months based on a negative inhibitor titre and having been transitioned to prophylaxis; at the time of data collection that patient was 13 months post completion of rFVIIIFc ITI and he continued to have a negative Bethesda titre on rFVIIIFc prophylaxis. A half-life ≥6 hours was also reported at that time. This patient had been on a three-times-per-week (50 IU/kg) ITI regimen.

Among these four patients, the median time to attain a negative Bethesda titre was 27.7 weeks (range: 4.1–64 weeks) and the median time to reported tolerization was 33.9 weeks (7.8 months; range: 21–64 weeks). For the three patients treated with daily rFVIIIFc, tolerization took only 29 weeks (6.7 months; range: 20.6–38 weeks), whereas it took 64 weeks (14.8 months) for the patient treated with a three-times-per-week ITI regimen.

Of the remaining patients (n=3), two had a decrease in Bethesda titre (from 32 to 18 BU and from 378 to 23 BU after 18 and 58 weeks of ITI, respectively), and one patient had an initial increase in Bethesda titre from 3 to 16 BU after 15 weeks. He was switched to ITI with another factor but remained unresponsive and after 27 weeks was resumed on rFVIIIFc ITI, which has now been ongoing for 7 weeks; his most recent Bethesda titre has fallen to 5 (**Table 1**). This patient was reported to be poorly compliant with ITI.

All seven first-time ITI patients continue on rFVIIIFc ITI or prophylaxis.

Rescue ITI patient outcomes

Seven of 12 previously failed patients undergoing rescue ITI (**Table 2**) achieved Bethesda negativity with rFVIIIFc ITI. Median time to attain a negative titre was 14.1 weeks (range: 3–67.6 weeks). Three of these seven patients remain Bethesda negative and continue on rFVIIIFc ITI (n=2) or have been weaned to rFVIIIFc prophylaxis (n=1). The other four patients who initially achieved a negative titre later developed a titre >0.6 BU. Of these, two continue on rFVIIIFc ITI and two were transitioned to ITI with other factors (**Table 2**).

Of the seven patients achieving Bethesda negativity, three also achieved normal FVIII recovery at 3, 14, and 65 weeks and a fourth patient reached normal FVIII half-life at 27 weeks. Recovery and half-life were not available in others (**Table 2**).

Of the remaining five of 12 rescue patients, one had a decrease in Bethesda titre (from 36 to 22 BU after 10 weeks) and in four, the Bethesda titre either remained unchanged or increased

while on ITI (**Table 2**). Of these five patients, four continue on rFVIIIFc ITI and one was removed from ITI and placed on bypass therapy alone.

Dosing outcomes, bypass agent use, and current treatment status

The patient population assessed in this study received a wide range/timing of doses (**Tables 1** and **2**). A trend toward rapid negative inhibitor titres was seen with higher doses administered daily. Five of five patients (one first-time ITI and four rescue ITI) who received a daily rFVIIIFc dose of ≥130 IU/kg achieved a negative Bethesda titre at a median of 28 weeks. Eighteen of 19 patients used bypass agents concurrently with rFVIIIFc ITI; fourteen were primarily on prophylaxis (9 with aPCCs and 5 with rFVIIa) and four were treated on demand with rFVIIa.

Overall, 16 of 19 patients remained on rFVIIIFc (prophylaxis or ITI) at the time of data collection.

Safety

No adverse events, including no thromboembolisms, were reported. Six surgeries were performed while patients were undergoing ITI under the cover of bypassing agents; all of them without interruption of rFVIIIFc ITI (knee synovectomy, intracranial neurosurgical evacuation, and four Port-A-Cath insertions). Inhibitor titres during surgeries were not collected for this study.

Discussion

Eradication of inhibitors using ITI is the gold standard for patients with HTI in haemophilia A and is the only therapy that can allow the patient to return to a prophylactic FVIII regimen. Studies have shown that long-term outcomes, including mortality, are greatly improved if inhibitors are eradicated and, furthermore, the long-term costs associated with inhibitor therapy would likely be reduced by early eradication [22, 33, 34].

The main limitations of ITI with conventional factor replacement therapies are the need for frequent factor infusions, which in most young children necessitates indwelling CVAD; the decreased quality of life while on ITI; and enormous healthcare utilization costs given the high doses of factor required [35]. All of these are compounded by the extended duration of treatment needed to achieve tolerization. If ITI required less time, then its drawbacks would be

greatly reduced. A FVIII product regimen that could successfully achieve a more rapid time to tolerization is key to clinical success and improving patient outcomes.

Registry data have indicated that inhibitor titre at start of ITI is a predictor of success, with titres <10 BU associated with better outcomes [36, 37]. Despite this, six of seven patients undergoing first-time ITI in this study started ITI with titres >10 BU. Four of these seven patients achieved inhibitor tolerization. ITI in these patients was started a median of 4.4 weeks from inhibitor diagnosis, without waiting for the inhibitor titre to drop to <10 BU.

Of late, the notion of inhibitor level >10 BU at start of ITI being considered a poor prognostic factor has been challenged, as very good success rates in patients starting ITI with inhibitor titres >10 BU have been reported when ITI has been commenced soon after inhibitor detection [17]. Conceivably, the quick initiation of ITI may have contributed to the success of ITI in this study. As there was evidence of rapid tolerization, an early ITI initiation approach with rFVIIIFc warrants prospective study.

A peak inhibitor titre >200 BU/mL is recognized as an independent risk factor for ITI failure [19, 36, 37]. All three patients in the first-time ITI group that had peak titres >200 BU/mL had a decrease in inhibitor titres after initiating rFVIIIFc ITI (**Table 1**). This includes a patient with a peak level of 1126 BU/mL who became Bethesda negative at 31 weeks and completely tolerized at 38 weeks. That patient has now transitioned to prophylaxis with rFVIIIFc. Lower-risk patient groups may benefit as well. Of the first-time ITI patients who were tolerized with a daily factor regimen, the individual with the lowest peak titre (51 BU) reached a negative Bethesda titre in 1 month and fully tolerized in 5 months, making them the fastest of all first-time patients to tolerize, highlighting a potential benefit of even faster inhibitor eradication in lower risk patients.

The rescue ITI patient group was a heavily pretreated cohort with an average number of prior ITI treatments of 2.6 and a median time from inhibitor diagnosis to start of rFVIIIFc ITI of 5.5 years. Despite this, rFVIIIFc demonstrated therapeutic benefit of inhibitor eradication in several of these patients. For example, one patient who failed five prior ITI regimens with different factors over a span of 5 years successfully reached a negative Bethesda titre and a normal FVIII recovery with rFVIIIFc ITI (FVIII half-life was not reported) and has now been weaned to rFVIIIFc prophylaxis. However, most rescue patients in this study were still undergoing rFVIIIFc ITI at the time of data collection and therefore a longer follow-up is needed to determine their final outcomes.

A variety of ITI protocols have been developed that include a wide range of dosing regimens [38]. In the International Immune Tolerance Induction Trial (I-ITI) [13], higher doses during ITI (200 IU/kg/day) achieved tolerization (negative Bethesda titre, normal FVIII recovery (≥66%) and half-life (≥6 hours) significantly faster than the low-dose regimen did (50 IU/kg three times per week). In this retrospective review, there was also a trend toward achieving a negative Bethesda titre faster with higher rFVIIIFc doses (≥130 IU/kg) administered on a daily basis.

In contrast to the first-time ITI rFVIIIFc–treated patients in this chart review, the I-ITI included first-time ITI patients with a more favourable risk profile. The median peak inhibitor titre for the I-ITI patients was 22 BU compared with 151 BU for the rFVIIIFc ITI patients presented here. The median titre at the start of ITI was 5.5 BU in the I-ITI as opposed to 52 BU for the rFVIIIFc ITI patients. In addition, the I-ITI excluded patients with peak titres >200 BU. In contrast, 43% of the first-time ITI patients in our cohort had peak titres >200 BU and 86% had a titre >10 BU at the start of rFVIIIFc ITI. Lastly, three of the seven first-time ITI patients reported here were of black race, which is associated with a lower rate of ITI success [39]. Based on the above, we speculate that the seven first-time ITI patients reported here constitute a select group of high-risk patients in whom clinicians tried rFVIIIFc hoping that it would be more successful than ITI using conventional FVIII products.

Although first-time ITI patients in our study were a higher-risk group for ITI failure (mainly on the basis of their high peak titres pre-ITI), four of the seven first-time patients still quickly achieved tolerization in a median of 7.8 months; in contrast, for the I-ITI study patients (who constituted a lower risk group for ITI failure), ITI took a median of 10.6 and 15.5 months (for high- and low-dose ITI regimens, respectively) to achieve tolerization [13].

A more comparable high-risk cohort of patients was evaluated by Oldenburg et al. [18] in which the use of a VWF-containing plasma-derived FVIII regimen for high-risk ITI patients was studied. The investigators reported a median time to tolerance of 20 months for high-risk first-time ITI patients, as measured via Kaplan-Meier method [18], which was higher than what was observed in our high-risk first-time ITI rFVIIIFc–treated patients. Because of the retrospective nature of our study, however, we recognize the limitations in comparing our data with these other cohorts.

We speculate that rFVIIIFc may have properties that uniquely promote tolerization [32]. In a mouse model of haemophilia A, rFVIIIFc had reduced immunogenicity, promoted FVIII-specific tolerance, and induced an increase in regulatory T cells and tolerance-related genes [31].

Furthermore, transplacental transfer of Fc fusion proteins with immunodominant A2 and C2 FVIII domains, as well as treatment with rFVIIIFc in haemophilia A mice, have been shown to induce tolerance and reduce immunogenicity in the progeny [29, 30]. In addition, epitopes in the Fc fragment are known to upregulate regulatory T cells, which can result in tipping the balance toward tolerance over immunogenicity [28]. These data are consistent with prior case reports in which four patients had been successfully treated with rFVIIIFc for inhibitors [27, 40] and with the case series described here.

ITI is a substantial economic burden in the healthcare utilization system, with high costs for both the FVIII and bypassing agents used. One study estimated that the average monthly costs were $78,000 for standard half-life FVIII and $25,000 for bypassing agents per month or $1.2 million per patient per year [35, 41]. What most impacts on the cost of ITI is its long duration. A US claims data analysis indicated that the real-world average duration of ITI with conventional FVIII products was 18.7 months [35]. The data presented in our study indicate that rFVIIIFc may offer a more rapid time to tolerization; this could in turn be associated with a potential decrease in long-term bypassing agent use and improvements in the excessive financial burden associated with ITI.

The main limitations of this study were its retrospective nature, its limited patient population and it being a case series which may lead to potential biases (including reporting bias). The relatively rapid achievement of tolerization in first-time ITI patients could be attributed to the use of rFVIIIFc but also could be due to the early initiation of ITI soon after inhibitor development. Because drawing definitive conclusions from a retrospective noncontrolled case series is not possible, clinical studies will be needed to generate these data in a prospective manner.

Conclusions

Collectively, our results show that ITI with rFVIIIFc is possible and can result in inhibitor eradication and successful ITI in many patients at high risk for ITI failure undergoing first-time ITI and in some patients undergoing rescue ITI. Furthermore, rFVIIIFc ITI demonstrated a rapid decrease in Bethesda titres and rapid time to tolerization in the majority of patients receiving first-time ITI despite their risk profile. For rescue ITI, it is more difficult to draw conclusions as most of these patients were still undergoing ITI with rFVIIIFc at the time of data collection. However, some patients receiving rescue ITI did appear to derive therapeutic benefit in that they either achieved Bethesda negativity or showed significant drops in inhibitor titres. This was particularly the case when higher rFVIIIFc dosing (≥130 IU/kg) was administered daily. These

findings highlight the need for additional data; two prospective trials are currently being initiated using rFVIIIFc for ITI in patients with haemophilia A with inhibitors (NCT03093480 and NCT03103542).

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Author contributions

Manuel Carcao, Amy Shapiro, Janice M. Staber, Nina Hwang, Colleen Druzgal, Ken Lieuw, Mark Belletrutti, Courtney D. Thornburg, Sanjay P. Ahuja, Jennifer Dumont, Gavin Miyasato, Nisha Jain, and Steven W. Pipe performed the research, analysed the data, and edited the manuscript. Jaime Morales-Arias and Elisa Tsao performed the research, analysed the data, and wrote the manuscript.

Disclosures

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Amy Shapiro has served on advisory boards for Shire, Bioverativ, Genentech, and Novo Nordisk and has been a consultant for Bioverativ, Kedrion Biopharma and Prometic Life Sciences. AS has been a board member for Novo Nordisk Haemophilia Foundation and participated in clinical research protocols for Shire, Bayer HealthCare, Bioverativ, Daiichi Sankyo, Kedrion Biopharma, Novo Nordisk, Octapharma, OPKO, Prometic Life Sciences, and PTC Therapeutics.

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Jaime Morales-Arias is an employee of and holds equity interest in Bioverativ.

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Gavin Miyasato is an employee of Trinity Partners LLC, a consulting firm retained by Bioverativ to conduct the study on which this manuscript was based.

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References

1. Mannucci PM, Tuddenham EG. The hemophilias--from royal genes to gene therapy. *The New England journal of medicine* 2001; **344:** 1773-9.
2. Lieuw K. Many factor VIII products available in the treatment of hemophilia A: an embarrassment of riches? *J Blood Med* 2017; **8:** 67-73.
3. Berntorp E, Shapiro AD. Modern haemophilia care. *The Lancet* 2012; **379:** 1447-56.
4. Pasi KJ, Rangarajan S, Georgiev P, Mant T, Creagh MD, Lissitchkov T*, et al.* Targeting of Antithrombin in Hemophilia A or B with RNAi Therapy. *The New England journal of medicine* 2017.
5. Peyvandi F, Garagiola I, Young G. The past and future of haemophilia: diagnosis, treatments, and its complications. *Lancet (London, England)* 2016; **388:** 187-97.
6. Gouw SC, van der Bom JG, Marijke van den Berg H. Treatment-related risk factors of inhibitor development in previously untreated patients with hemophilia A: the CANAL cohort study. *Blood* 2007; **109:** 4648-54.
7. Darby SC, Keeling DM, Spooner RJ, Wan Kan S, Giangrande PL, Collins PW*, et al.* The incidence of factor VIII and factor IX inhibitors in the hemophilia population of the UK and their effect on subsequent mortality, 1977-99. *Journal of thrombosis and haemostasis : JTH* 2004; **2:** 1047-54.
8. DiMichele DM, Hoots WK, Pipe SW, Rivard GE, Santagostino E. International workshop on immune tolerance induction: consensus recommendations. *Haemophilia : the official journal of the World Federation of Hemophilia* 2007; **13 Suppl 1:** 1-22.
9. Oldenburg J, Mahlangu JN, Kim B, Schmitt C, Callaghan MU, Young G*, et al.* Emicizumab Prophylaxis in Hemophilia A with Inhibitors. *New England Journal of Medicine* 2017; **0:** null.
10. Wight J, Paisley S, Knight C. Immune tolerance induction in patients with haemophilia A with inhibitors: a systematic review. *Haemophilia : the official journal of the World Federation of Hemophilia* 2003; **9:** 436-63.
11. Coppola A, Margaglione M, Santagostino E, Rocino A, Grandone E, Mannucci PM*, et al.* Factor VIII gene (F8) mutations as predictors of outcome in immune tolerance induction of hemophilia A patients with high-responding inhibitors. *Journal of thrombosis and haemostasis : JTH* 2009; **7:** 1809-15.
12. Gringeri A, Musso R, Mazzucconi MG, Piseddu G, Schiavoni M, Pignoloni P*, et al.* Immune tolerance induction with a high purity von Willebrand factor/VIII complex concentrate in haemophilia A patients with inhibitors at high risk of a poor response. *Haemophilia : the official journal of the World Federation of Hemophilia* 2007; **13:** 373-9.

13. Hay CR, DiMichele DM, International Immune Tolerance S. The principal results of the International Immune Tolerance Study: a randomized dose comparison. *Blood* 2012; **119:** 1335-44.
14. Haya S, Lopez MF, Aznar JA, Batlle J, Spanish Immune Tolerance G. Immune tolerance treatment in haemophilia patients with inhibitors: the Spanish Registry. *Haemophilia : the official journal of the World Federation of Hemophilia* 2001; **7:** 154-9.
15. Jimenez-Yuste V, Oldenburg J, Rangarajan S, Kurth MH, Bozzo J, Santagostino E. Clinical overview of Fanhdi/Alphanate (plasma-derived, VWF-containing FVIII concentrate) in immune tolerance induction in haemophilia A patients with inhibitors. *Haemophilia : the official journal of the World Federation of Hemophilia* 2016; **22:** e71-4.
16. Kreuz W, Escuriola Ettingshausen C, Vdovin V, Zozulya N, Plyushch O, Svirin P*, et al.* First prospective report on immune tolerance in poor risk haemophilia A inhibitor patients with a single factor VIII/von Willebrand factor concentrate in an observational immune tolerance induction study. *Haemophilia : the official journal of the World Federation of Hemophilia* 2016; **22:** 87-95.
17. Nakar C, Manco-Johnson MJ, Lail A, Donfield S, Maahs J, Chong Y*, et al.* Prompt immune tolerance induction at inhibitor diagnosis regardless of titre may increase overall success in haemophilia A complicated by inhibitors: experience of two U.S. centres. *Haemophilia : the official journal of the World Federation of Hemophilia* 2015; **21:** 365-73.
18. Oldenburg J, Jimenez-Yuste V, Peiro-Jordan R, Aledort LM, Santagostino E. Primary and rescue immune tolerance induction in children and adults: a multicentre international study with a VWF-containing plasma-derived FVIII concentrate. *Haemophilia : the official journal of the World Federation of Hemophilia* 2014; **20:** 83-91.
19. DiMichele DM, Kroner BL, North American Immune Tolerance Study G. The North American Immune Tolerance Registry: practices, outcomes, outcome predictors. *Thromb Haemost* 2002; **87:** 52-7.
20. Antun A, Monahan PE, Manco-Johnson MJ, Callaghan MU, Kanin M, Knoll C*, et al.* Inhibitor recurrence after immune tolerance induction: a multicenter retrospective cohort study. *Journal of thrombosis and haemostasis : JTH* 2015; **13:** 1980-8.
21. Valentino LA, Kempton CL, Kruse-Jarres R, Mathew P, Meeks SL, Reiss UM*, et al.* US Guidelines for immune tolerance induction in patients with haemophilia a and inhibitors. *Haemophilia : the official journal of the World Federation of Hemophilia* 2015; **21:** 559-67.
22. Walsh CE, Jimenez-Yuste V, Auerswald G, Grancha S. The burden of inhibitors in haemophilia patients. *Thromb Haemost* 2016; **116 Suppl 1:** S10-7.

23. Mahlangu J, Powell JS, Ragni MV, Chowdary P, Josephson NC, Pabinger I*, et al.* Phase 3 study of recombinant factor VIII Fc fusion protein in severe hemophilia A. *Blood* 2014; **123:** 317-25.

24. Shapiro AD, Mahlangu JN, Perry D, Pasi J, Quon DV, Chowdary P*, et al.* Treatment of bleeding episodes with recombinant factor VIII Fc fusion protein in A-LONG study subjects with severe haemophilia A. *Haemophilia : the official journal of the World Federation of Hemophilia* 2017; **23:** 392-9.

25. Nolan B, Mahlangu J, Perry D, Young G, Liesner R, Konkle B*, et al.* Long-term safety and efficacy of recombinant factor VIII Fc fusion protein (rFVIIIFc) in subjects with haemophilia A. *Haemophilia : the official journal of the World Federation of Hemophilia* 2016; **22:** 72-80.

26. Young G, Mahlangu J, Kulkarni R, Nolan B, Liesner R, Pasi J*, et al.* Recombinant factor VIII Fc fusion protein for the prevention and treatment of bleeding in children with severe hemophilia A. *Journal of thrombosis and haemostasis : JTH* 2015; **13:** 967-77.

27. Malec LM, Journeycake J, Ragni MV. Extended half-life factor VIII for immune tolerance induction in haemophilia. *Haemophilia : the official journal of the World Federation of Hemophilia* 2016; **22:** e552-e4.

28. De Groot AS, Moise L, McMurry JA, Wambre E, Van Overtvelt L, Moingeon P*, et al.* Activation of natural regulatory T cells by IgG Fc-derived peptide "Tregitopes". *Blood* 2008; **112:** 3303-11.

29. Gupta N, Culina S, Meslier Y, Dimitrov J, Arnoult C, Delignat S*, et al.* Regulation of immune responses to protein therapeutics by transplacental induction of T cell tolerance. *Sci Transl Med* 2015; **7:** 275ra21.

30. Georgescu M LT, Sponagle K, Hebert K, Drager D, Patarroyo-White S, Hough C, Jiang H, Lillicrap D. Factor VIII tolerance induction in haemophilia a mice via transplacental transfer of recombinant factor VIII Fc. *Journal of Thrombosis and Haemostasis* 2015; **13:** 1-997.

31. Krishnamoorthy S, Liu T, Drager D, Patarroyo-White S, Chhabra ES, Peters R*, et al.* Recombinant factor VIII Fc (rFVIIIFc) fusion protein reduces immunogenicity and induces tolerance in hemophilia A mice. *Cell Immunol* 2016; **301:** 30-9.

32. Kis-Toth K SA, Henry K, Loh C. Poster Presentations. *Haemophilia : the official journal of the World Federation of Hemophilia* 2017; **23:** 29-140.

33. Jimenez-Yuste V, Oldenburg J, Rangarajan S, Peiro-Jordan R, Santagostino E. Long-term outcome of haemophilia A patients after successful immune tolerance induction therapy using a single plasma-derived FVIII/VWF product: the long-term ITI study. *Haemophilia : the official journal of the World Federation of Hemophilia* 2016; **22:** 859-65.

34. Rocino A, Franchini M, Coppola A. Treatment and Prevention of Bleeds in Haemophilia Patients with Inhibitors to Factor VIII/IX. *J Clin Med* 2017; **6**.

35. Su J ZJ, Buckley B, Rising T, Hou Q, Jain N. The Immune Tolerance Induction Factor Utilizations and Costs for the Management of Male Hemophilia-a Patients Who Developed Inhibitors. *ASH* 2016; **128:** P4758.

36. Mariani G, Kroner B, Immune Tolerance Study G. Immune tolerance in hemophilia with factor VIII inhibitors: predictors of success. *Haematologica* 2001; **86:** 1186-93.

37. Minno GD, Santagostino E, Pratt K, Königs C. New predictive approaches for ITI treatment. *Haemophilia : the official journal of the World Federation of Hemophilia* 2014; **20:** 27-43.

38. Kempton CL, White GC, 2nd. How we treat a hemophilia A patient with a factor VIII inhibitor. *Blood* 2009; **113:** 11-7.

39. Callaghan MU, Rajpurkar M, Chitlur M, Warrier I, Lusher J. Immune tolerance induction in 31 children with haemophilia A: is ITI less successful in African Americans? *Haemophilia : the official journal of the World Federation of Hemophilia* 2011; **17:** 483-9.

40. Groomes CL, Gianferante DM, Crouch GD, Parekh DS, Scott DW, Lieuw K. Reduction of Factor VIII Inhibitor Titers During Immune Tolerance Induction With Recombinant Factor VIII-Fc Fusion Protein. *Pediatr Blood Cancer* 2016; **63:** 922-4.

41. Su J ZJ, Buckley B, Hou Q, Jain N. Utilizations and Costs of Bypass Therapies for the Management of Hemophilia A Patients with Inhibitors. *Haemophilia : the official journal of the World Federation of Hemophilia* 2017; **23:** 87-8.

Table 1 Patients receiving ITI for the first time

Pt	Age (yr); Race	FVIII genotype	Inhibitor titer (BU): Historical peak	Inhibitor titer (BU): Pre-rFVIIIFc ITI	Time from inhibitor diagnosis to start of rFVIIIFc ITI (wk)	rFVIIIFc ITI regimen	Time to (wk): Negative Bethesda titre	Time to (wk): Normal recovery	Time to (wk): Tolerization	Duration of ongoing rFVIIIFc ITI (wk)	Current titre (BU)	Current status
1	4.3; white	Missense	51.7	51.7	10.9	85 IU/kg/day	4.1	9.7	20.6	Tolerized	<0.6	rFVIIIFc prophylaxis
2	1; black	Frameshift	150.9	106.9	13	100 IU/kg/day	24.4	29.4	29.4	Tolerized	<0.6	rFVIIIFc prophylaxis
3	1.4; white	N/R	1126	1126	1.1	200 IU/kg/day	31	36	38.3	Tolerized	<0.6	rFVIIIFc prophylaxis
4	1.3; black	I-22[b]	11	11	4.4	50 IU/kg 3/wk	64	N/R	64	Tolerized	<0.6	rFVIIIFc prophylaxis
5	2.1; black	I-22	388	32	41	102 IU/kg EOD	N/A	N/A	N/A	18.4	18	rFVIIIFc ITI
6	0.97; white	I-22	378.7	378.1	1	96 IU/kg/day	N/A	N/A	N/A	58.1	22.6	rFVIIIFc ITI
7	0.81; Asian	I-22	30	3	0	83 IU/kg/day	N/A	N/A	N/A	7	5	rFVIIIFc ITI

Notes: Pt, Patient; BU, Bethesda units; EOD, every other day; I-22, intron 22 inversion; ITI, immune tolerance induction; N/R, not reported; N/A, not applicable; rFVIIIFc, recombinant factor VIII Fc fusion protein.

Time to tolerization based on physician report, resolved Bethesda titre, normal recovery, and half-life (≥6 hours). Pt 4 did not have recovery and half-life information available but was reported as tolerized by physician and switched to rFVIIIFc prophylaxis.

[a]Initially treated with rFVIIIFc ITI, had increased titer to 16 BU after 15 weeks and was switched to another factor ITI for 27 weeks with lack of response. Now re-started on rFVIIIFc ITI for 7 weeks. Received concomitant rituximab (4 weekly doses, initiated 3 weeks after re-starting rFVIIIFc ITI).

[b]Based on sibling's genotype.

Table 2 Patients receiving rescue ITI

Pt	Age (yr); Race	FVIII Genotype	Number of prior ITI regimens	Inhibitor titer (BU)		Time from inhibitor diagnosis to start of rFVIIIFc ITI (wk)	rFVIIIFc ITI regimen	Time to (wk)			Duration on rFVIIIFc ITI (wk)	Current titre (BU/mL)	Current status
				Historical peak	Pre-rFVIIIFc ITI			Negative Bethesda titre[b]	Normal recovery	Tolerization			
8	6.5; white	I-22	5	250	9	296.9	202 IU/kg/day	27.9	65.3	N/R	79.9	<0.6	rFVIIIFc prophylaxis
9[a,c]	4.8; white	I-22	2	67	4	249	150 IU/kg/day	3	3	N/R	40.7	<0.6	Other factor ITI
10	11; white	Large deletion	2	70	35	498.1	200 IU/kg EOD	31.4	N/R	N/R	31.4	<0.6	rFVIIIFc ITI
11	2.7; black	I-22	1	178	1	93	100 IU/kg 3x/wk	14.1	N/R	27.4	38.4	<0.6	rFVIIIFc ITI
12[a,d]	1.6; white	I-22	2	460	200	41.6	150 IU/kg/day	13	14	N/R	91	2	Other factor ITI
13	5.5; white	I-22	3	41.8	22.3	264.6	130 IU/kg/day	67.6	N/R	N/R	131.1	15.8	rFVIIIFc ITI
14[a]	6.1; white	Nonsense	2	306	128.5	243.1	100 IU/kg/day	12.9	N/R	N/R	41.1	23	rFVIIIFc ITI
15	6.3; white	I-22	1	35	36	271.4	200 IU/kg EOD	N/A	N/A	N/A	9.6	22	rFVIIIFc ITI
16	12.6; white	I-22	3	11	1.3	625.9	100 IU/kg EOD	N/A	N/A	N/A	56.3	0.9	rFVIIIFc ITI
17	9.3; other	I-22	2	8	0.6	439.1	115 IU/kg EOD	N/A	N/A	N/A	22.3	1.2	rFVIIIFc ITI
18	9.1; white	Large deletion	4	1024	237	473.1	100 IU/kg/day	N/A	N/A	N/A	38	1024	rFVIIIFc ITI
19	11.3; white	Nonsense	4	409	26	491	100 IU/kg/day	N/A	N/A	N/A	93.7	166	Bypass therapy

Notes: Pt, Patient; BU, Bethesda units; EOD, every other day; I-22, intron 22 inversion; ITI, immune tolerance induction; N/R, not reported; N/A, not applicable; rFVIIIFc, recombinant factor VIII Fc fusion protein.
Tolerization defined as achieving a half-life of ≥6 hours

[a]Pts 9, 12, and 14 received concomitant rituximab (Pt 9: 6 weekly doses, started 11 weeks before initiating rFVIIIFc ITI; Pt 12: 4 weekly doses, started 5 weeks after initiating rFVIIIFc ITI; Pt 14: 4 weekly doses, started 38 weeks after initiating rFVIIIFc ITI); [b]Time to negative Bethesda titre represents time from start of rFVIIIFc ITI to first report of negative titre.

Additional Details:

[c]Pt 9 achieved negative Bethesda titre and normal FVIII recovery 3 weeks after starting rFVIIIFc ITI; switched to other factor ITI after 40.7 weeks on rFVIIIFc ITI due to positive titre (9 BU), and with a FVIII recovery of 22% at the time.

[d]Pt 12 achieved negative Bethesda titre and normal FVIII recovery 13 and 14 weeks after starting rFVIIIFc ITI, respectively; switched to other factor ITI after 91 weeks on rFVIIIFc ITI due to positive titre (2 BU).