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3-1-2018

Recombinant factor VIII Fc fusion protein for immune tolerance induction in patients with severe haemophilia A with inhibitors-A retrospective analysis

M Carcao

A Shapiro

J M. Staber
University of Iowa

Please see article for additional authors.

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Comments

This study was sponsored by Bioverativ Therapeutics, Inc. (Waltham, MA). Medical writing and editorial support were provided by Ashleigh Pulkoski-Gross, PhD (Fishawack Communications, Conshohocken, PA) and Santo D'Angelo, PhD (Fishawack Communications, Conshohocken, PA), which was funded by Bioverativ Therapeutics, Inc. (Waltham, MA).

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Accepted: 4 January 2018

DOI: 10.1111/hae.13413

ORIGINAL ARTICLE

Clinical haemophilia

WILEY Haemophilia

Recombinant factor VIII Fc fusion protein for immune tolerance induction in patients with severe haemophilia A with inhibitors—A retrospective analysis

M. Carcao[1] | A. Shapiro[2] | J. M. Staber[3] | N. Hwang[4] | C. Druzgal[5] | K. Lieuw[6] | M. Belletrutti[7] | C. D. Thornburg[8] | S. P. Ahuja[9] | J. Morales-Arias[10] | J. Dumont[10] | G. Miyasato[11] | E. Tsao[10] | N. Jain[10] | S. W. Pipe[12]

[1]Division of Haematology/Oncology, Department of Paediatrics, Child Health Evaluative Sciences, Research Institute, Hospital for Sick Children, Toronto, ON, Canada

[2]Indiana Hemophilia & Thrombosis Center, Indianapolis, IN, USA

[3]University of Iowa Stead Family Children's Hospital, Iowa City, IA, USA

[4]Center for Inherited Blood Disorders, Orange, CA, USA

[5]University of Virginia Health System, Charlottesville, VA, USA

[6]Walter Reed National Military Medical Center, Bethesda, MD, USA

[7]University of Alberta Stollery Children's Hospital, Edmonton, AB, Canada

[8]Rady Children's Hospital San Diego, San Diego, CA, USA

[9]University Hospitals Rainbow Babies and Children's Hospital, Cleveland, OH, USA

[10]Bioverativ Therapeutics, Inc., Waltham, MA, USA

[11]Trinity Partners LLC, Waltham, MA, USA

[12]University of Michigan, Ann Arbor, MI, USA

Correspondence
Manuel Carcao, Division of Haematology/Oncology; Room 9416, The Hospital for Sick Children, Division of Haematology/Oncology, Toronto, ON, Canada.
Tel. 416 813 5367; Fax: 416 813 5327
Email: manuel.carcao@sickkids.ca

Funding information
Bioverativ Therapeutics, Inc.

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 recombinant factor VIII Fc fusion protein (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, 7 were first-time ITI and 12 were rescue ITI. Of 7 first-time patients, 6 had at least 1 high-risk feature for ITI failure. Four of 7 first-time patients were tolerized in a median of 7.8 months. The remaining 3 patients continue on rFVIIIFc ITI. Of 12 rescue patients, 7 initially achieved a negative Bethesda titre (≤0.6) in a median of 3.3 months, 1 had a decrease in Bethesda titre and continues on rFVIIIFc ITI and 4 have not demonstrated a decrease in Bethesda titre. Of these 4, 3 continue on rFVIIIFc ITI and 1 switched to bypass therapy alone. Two initially responsive patients transitioned to other factors due to recurrence. Overall, 16 of 19 patients remain on rFVIIIFc (prophylaxis or ITI). For those still undergoing ITI, longer follow-up is needed to determine final outcomes. No adverse events reported.

Conclusions: Recombinant factor VIII Fc fusion protein 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.

KEYWORDS

haemophilia A, immune tolerance induction, inhibitor, recombinant factor VIII Fc fusion protein, rescue therapy, retrospective chart review

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1 | 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%-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 1-2 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 3 patients with haemophilia A using rFVIIIFc for ITI (in 1 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.

2 | MATERIALS AND METHODS

A non-interventional 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 1 July 2014 and 1 June 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 evaluated for risk factors 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.

3 | RESULTS

3.1 | Study population

Nineteen patients were identified. Of these, 7 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 5 of 7 first-time ITI patients and 11 of 12 rescue ITI patients. Of first-time ITI patients, 3 were black, 3 were white, and 1 was Asian. For the rescue ITI patients, the majority were white (10/12), 1 was black, and 1 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, 6 of 7 first-time ITI patients had titres >10 BU; 4 of these 6 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.

3.2 | First-time ITI patient outcomes

At the time of data collection, 4 of 7 patients undergoing first-time ITI with rFVIIIFc (Table 1) were tolerized and had transitioned to rFVIIIFc prophylaxis. Three of these 4 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

TABLE 1 Patients receiving ITI for the first time

Pt	Age (y); race	FVIII genotype	Inhibitor titre (BU)		Time from inhibitor diagnosis to start of rFVIIIFc ITI (wk)	rFVIIIFc ITI regimen	Time to (wk)		Tolerization	Duration of rFVIIIFc ITI (wk)	Current titre (BU)	Current status
			Historical peak	Pre-rFVIIIFc ITI			Negative Bethesda titre	Normal recovery				
1	4.3; white	Missense	51.7	51.7	10.9	85 IU/kg/d	4.1	9.7	20.6	Tolerized	<0.6	rFVIIIFc prophylaxis
2	1; black	Frameshift	150.9	106.9	13	100 IU/kg/d	24.4	29.4	29.4	Tolerized	<0.6	rFVIIIFc prophylaxis
3	1.4; white	N/R	1126	1126	1.1	200 IU/kg/d	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/d	N/A	N/A	N/A	58.1	22.6	rFVIIIFc ITI
7[a]	0.81; Asian	I-22	30	3	0	83 IU/kg/d	N/A	N/A	N/A	7	5	rFVIIIFc ITI

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

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.

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

[b]Based on sibling's genotype.

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 3-times-per-week (50 IU/kg) ITI regimen.

Among these 4 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 3 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 3-times-per-week ITI regimen.

Of the remaining patients (n = 3), 2 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 1 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 7 first-time ITI patients continue on rFVIIIFc ITI or prophylaxis.

3.3 | 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 7 patients remain Bethesda negative and continue on rFVIIIFc ITI (n = 2) or have been weaned to rFVIIIFc prophylaxis (n = 1). The other 4 patients who initially achieved a negative titre later developed a titre >0.6 BU. Of these, 2 continue on rFVIIIFc ITI and 2 were transitioned to ITI with other factors (Table 2).

Of the 7 patients achieving Bethesda negativity, 3 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 5 of 12 rescue patients, one had a decrease in Bethesda titre (from 36 to 22 BU after 10 weeks) and in 4, the Bethesda titre either remained unchanged or increased while on ITI (Table 2). Of these 5 patients, 4 continue on rFVIIIFc ITI and 1 was removed from ITI and placed on bypass therapy alone.

3.4 | 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 towards rapid negative inhibitor titres was seen with higher doses administered daily. Five of 5 patients (1 first-time ITI and 4 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; 14 were primarily on prophylaxis (9 with aPCCs and 5 with rFVIIa), and 4 were treated on demand with rFVIIa.

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

3.5 | 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 4 Port-A-Cath insertions). Inhibitor titres during surgeries were not collected for this study.

4 | 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, 6 of 7 patients undergoing first-time ITI in this study started ITI with titres >10 BU. Four of these 6 patients achieved inhibitor tolerization. ITI in all 7 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 3 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 5 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/d) achieved tolerization (negative Bethesda titer, normal FVIII recovery [≥66%] and half-life [≥6 hours]) significantly faster than the low-dose regimen did (50 IU/kg 3 times per week). In this retrospective review, there was also a trend towards 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, 3 of the 7 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 7 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), 4 of the 7 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

TABLE 2 Patients receiving rescue ITI

Pt	Age (y); race	FVIII genotype	Number of prior ITI regimens	Inhibitor titre (BU)		Time from inhibitor diagnosis to start of rFVIIIFc ITI (wk)	rFVIIIFc ITI regimen	Time to (wk)			Duration of rFVIIIFc ITI (wk)	Current titre (BU)	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/d	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/d	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/d	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/d	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/d	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/d	N/A	N/A	N/A	38	1024	rFVIIIFc ITI
19	11.3; white	Nonsense	4	409	26	491	100 IU/kg/d	N/A	N/A	N/A	93.7	166	Bypass therapy

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 h.

[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.

[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).

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, has 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 towards tolerance over immunogenicity.[28] These data are consistent with prior case reports in which 4 patients had been successfully treated with rFVIIIFc for inhibitors[27,40] and with the case series described here.

Immune tolerance induction 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 of ITI were $103,000 ($78,000 for standard half-life FVIII and $25,000 for bypassing agents) 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 non-controlled case series is not possible, clinical studies will be needed to generate these data in a prospective manner.

5 | 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; 2 prospective trials are currently being initiated using rFVIIIFc for ITI in patients with haemophilia A with inhibitors (NCT03093480 and NCT03103542).

ACKNOWLEDGEMENTS

This study was sponsored by Bioverativ Therapeutics, Inc. (Waltham, MA). Medical writing and editorial support were provided by Ashleigh Pulkoski-Gross, PhD (Fishawack Communications, Conshohocken, PA) and Santo D'Angelo, PhD (Fishawack Communications, Conshohocken, PA), which was funded by Bioverativ Therapeutics, Inc. (Waltham, MA).

DISCLOSURES

Manuel Carcao has received honoraria for participation in advisory boards, speaker fees and research support from Baxalta/Shire, Bayer, Biogen/Bioverativ, Biotest, CSL Behring, Grifols, Novo Nordisk, Octapharma, Pfizer and Roche. Amy Shapiro has served on advisory boards for Shire, Bioverativ, Genentech and Novo Nordisk; has been a consultant for Bioverativ, Kedrion Biopharma and Prometic Life Sciences and has participated in clinical research protocols for Shire, Bayer HealthCare, Bioverativ, Daiichi Sankyo, Kedrion Biopharma, Novo Nordisk, Octapharma, OPKO, Prometic Life Sciences and PTC Therapeutics. Janice M. Staber has received honoraria from HEMA Biologics and Emergent BioSolutions. Nina Hwang has served on advisory boards for Bayer and Baxalta/Shire and has been an investigator for studies funded by Bioverativ. Colleen Druzgal has no disclosures to make. Ken Lieuw has no disclosures to make. Mark Belletrutti has served on advisory boards for Bioverativ, Roche Canada, Shire and Octapharma Canada and has received travel support from Octapharma Canada and Shire. Courtney D. Thornburg has served as a paid member of a DSMC for Bioverativ and has received funding from Bioverativ for research carried out in this work. Sanjay P. Ahuja has served on advisory boards for Bayer, Shire, CSL Behring, Novo Nordisk and Bioverativ and has been an investigator for clinical research trials for Shire, Bayer, Novo Nordisk and Pfizer. Jaime Morales-Arias is an employee of and holds equity interest in Bioverativ. Jennifer Dumont is an employee of and holds equity interest in Bioverativ. 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. Elisa Tsao is an employee of and holds equity interest in Bioverativ. Nisha Jain is an employee of and holds equity interest in Bioverativ. Steven Pipe has served as a consultant to Bioverativ.

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, wrote and, or edited the manuscript. Jaime Morales-Arias and Elisa Tsao performed the research, analysed the data and wrote the manuscript.

ORCID

M. Carcao http://orcid.org/0000-0001-5350-1763

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How to cite this article: Carcao M, Shapiro A, Staber JM, et al. Recombinant factor VIII Fc fusion protein for immune tolerance induction in patients with severe haemophilia A with inhibitors—A retrospective analysis. *Haemophilia*. 2018;24:245–252. https://doi.org/10.1111/hae.13413