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LETTER TO THE EDITOR

Real-world data of immune tolerance induction using recombinant factor VIII Fc fusion protein in patients with severe haemophilia A with inhibitors at high risk for immune tolerance induction failure: A follow-up retrospective analysis

Dear Editor,

Prophylactic factor VIII (FVIII) replacement is the current standard of care for severe haemophilia A but approximately 25%–40% of patients develop inhibitors against exogenous FVIII, rendering FVIII replacement therapy ineffective.[1] Eradication of high-titre inhibitors involves immune tolerance induction (ITI): repeated, long-term administration of high-dose FVIII.[1]

Recombinant FVIII Fc fusion protein (rFVIIIFc [ELOCTATE®, Sanofi, Waltham, MA]) is the first extended half-life FVIII approved for haemophilia A.[2] Case reports and an initial retrospective chart review suggest that rFVIIIFc ITI may lead to faster tolerization than ITI with standard FVIII concentrates.[3,4] This letter reports final clinical outcomes of 29 patients (19 included in the initial analysis) with severe haemophilia A undergoing ITI with rFVIIIFc in a real-world setting.[4]

We performed a retrospective review of patient charts at 13 sites across the United States and Canada, using previously published methods.[4] Briefly, de-identified clinical data were collected from patients with severe haemophilia A and historical high-titre inhibitors, who began first-time or rescue ITI with rFVIIIFc between July 2014 and February 2018 and had ≥3 months of exposure to rFVIIIFc ITI. Rescue ITI patients were defined as patients who had failed at least one previous ITI attempt. Tolerization was defined as a negative Bethesda titre (<0.6 BU/mL), normal FVIII recovery (≥66% of expected) and rFVIIIFc half-life ≥6 hours.[5]

Altogether, 29 rFVIIIFc ITI patients were identified: 10 first-time (Table 1) and 19 rescue patients (Table 2). Median (range) age at initiation of rFVIIIFc ITI was 1.4 (0.4–4.3) years for first-time and 6.5 (1.6–48.9) years for rescue patients. Of the 10 first-time ITI patients, 3 had peak inhibitor titres >200 BU/mL (accepted risk factor for ITI failure), while 8 had inhibitor titres >10 BU/mL at ITI start (traditionally considered a risk factor for ITI failure, although many clinicians are disputing this).[1] All rescue ITI patients were considered high risk for ITI failure; all had previously undergone ITI, 9 had peak inhibitor titres >200 BU/mL and 16 had an inhibitor for >2 years.

First-time ITI patients had median (range) historical peak inhibitor titre of 45.1 (3.0–1126.0) BU/mL and median (range) time from inhibitor diagnosis to start of rFVIIIFc ITI of 6.4 (0.0–41.0) weeks. Median (range) inhibitor titre at start of rFVIIIFc ITI was 28.8 (3.0–1126.0) BU/mL. Dosing regimens for rFVIIIFc ITI varied; median (range) dose was 100 (50–200) IU/kg and median (range) weekly dose was 700 (150–1400) IU/kg. One first-time ITI patient received rituximab during rFVIIIFc ITI.

Rescue ITI patients had median (range) historical peak inhibitor titre of 110.0 (8.0–1178.0) BU/mL, median (range) time from inhibitor diagnosis to start of rFVIIIFc ITI of 296.9 (31.6–2242.4) weeks (5.7 [0.6–43.0] years), had undergone a median (range) of 2 (1–7) prior ITI courses and had median (range) inhibitor titre at start of rFVIIIFc ITI of 22.3 (0.6–237.0) BU/mL. Dosing regimens for rFVIIIFc ITI varied; median (range) dose was 100 (43–200) IU/kg and median (range) weekly dose was 700 (129–1400) IU/kg. Three rescue patients received rituximab during rFVIIIFc ITI.

Nine out of 10 patients receiving first-time ITI using rFVIIIFc (including the patient who received rituximab) achieved a negative Bethesda titre at a median (range) of 30 (3–99) weeks (mean [standard deviation (SD)]: 34.0 [31.2] weeks), achieved tolerance at a median (range) of 30 (3–99) weeks (mean [SD]: 41 [29] weeks) and 8 transitioned to rFVIIIFc prophylaxis. One patient who achieved Bethesda negativity and was considered by their physician to be tolerized showed a low-titre inhibitor (1.3 BU/mL) during the follow-up period; this patient remained on rFVIIIFc ITI at the time of data capture. The tenth patient had a decreased Bethesda titre from 6.2 BU/mL at the start of rFVIIIFc to 4.4 BU/mL at 59 weeks and continued on rFVIIIFc ITI.

Over half (10/19) of the patients receiving rescue ITI reached a negative Bethesda titre after a median (range) of 21 (3–100) weeks (mean [SD]: 35.3 [32.6] weeks); 4 were subsequently tolerized (at 22,

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35, 47 and 101 weeks; 3 of these transitioned to rFVIIIFc prophylaxis and 1 relapsed and returned to rFVIIIFc ITI), 3 were on emicizumab at the time of data capture, 1 was tolerized on another FVIII product and afterwards transitioned to rFVIIIFc prophylaxis and 2 continued rFVIIIFc ITI. Of the 9 rescue patients who had not reached a negative Bethesda titre at the time of data capture, 4 remained on rFVIIIFc ITI; 5 stopped rFVIIIFc ITI and transitioned to either emicizumab (n = 2), prophylaxis with a bypass agent (n = 2) or prophylaxis with another FVIII replacement therapy and bypass agent (n = 1).

Altogether, 24/29 patients (9 first-time, 15 rescue) had a central venous access device in place before commencing rFVIIIFc ITI. Most patients (19/29 [66%]: 9 first-time, 10 rescue) began rFVIIIFc ITI on a daily dosing regimen, ranging from 83 to 200 IU/kg daily. Twelve (41%) patients changed their ITI dosing regimen at some point. Most

TABLE 1 First-time ITI patients[†‡]

		Inhibitor titre (BU/mL)				
Patient	**FVIII genotype**	**Historical peak (pre-ITI)**	**Immediately pre-rFVIIIFc ITI**	**Factor brand being used when inhibitor developed**	**rFVIIIFc ITI regimen**	**Weekly factor usage (IU/kg)**
1-9[§§]	Intron−22	38.4	**20.8**	rFVIIIFc (Eloctate, Sanofi, Waltham, MA)	200 IU/kg q.d.	1400
1-1	Missense	51.7	**51.7**	rFVIIIFc (Eloctate, Sanofi, Waltham, MA)	85 IU/kg q.d.	595
1-8[§§]	Intron−22	25.6	**25.6**	rFVIIIFc (Eloctate, Sanofi, Waltham, MA)	200 IU/kg q.d.	1400
1-2	Frameshift	150.9	**106.9**	pdFVIII (Alphanate, Grifols Biologicals LLC, Los Angeles, CA)	110 IU/kg q.d.	770
1-5	Intron−22	**376.0**	**32.0**	rFVIII (Advate, Baxalta US Inc, Lexington, MA)	100 IU/kg q.d.	700
1-3	Unknown	**1126.0**	**1126.0**	rFVIII (Advate, Baxalta US Inc, Lexington, MA)	200 IU/kg q.d.	1400
1-7[¶¶,†††]	Intron−22	3.0[‡‡‡]	3.0	rFVIIIFc (Eloctate, Sanofi, Waltham, MA)	83 IU/kg q.d.	581
1-4[§§§]	Intron−22	11.0	**11.0**	rFVIII (Xyntha, Pfizer, Philadelphia, PA)	50 IU/kg t.i.w.	150
1-6	Intron−22	**378.7**	**378.1**	rFVIII (Advate, Baxalta US Inc, Lexington, MA)	96 IU/kg q.d.	672
1-10[§§]	Insertion	28.8	6.2	Missing data	100 IU/kg q.d.	700

Abbreviations: BU, Bethesda unit; FVIII, factor VIII; ITI, immune tolerance induction; N/A, not applicable; NR, not reported; q.d., once daily; rFVIIIFc, recombinant factor VIII Fc fusion protein; t.i.w., three times per week.

[†]Patients are sorted in ascending order according to time from the start of ITI to tolerization. Patient numbers were randomly assigned.

[‡]Bolded data indicate high-risk features.

[§]Time to first negative inhibitor titre: time interval (in weeks) from the start date of ITI treatment with rFVIIIFc to date of the patient's first time reaching inhibitor titre of <0.6 BU/mL.

[¶]Time to FVIII normal recovery: time interval (in weeks) from the date of ITI treatment with rFVIIIFc to date of the patient's first time reaching FVIII recovery level of ≥66% of expected.

[††]Time to FVIII half-life of ≥6 hours: time interval (in weeks) from the start date of ITI treatment with rFVIIIFc to date of the patient's first time reaching FVIII half-life of ≥6 hours.

[‡‡]Time to tolerization: time interval (in weeks) from the start date of ITI treatment with rFVIIIFc to the date when physician reported this patient reached tolerization.

[§§]Newly identified patient.

[¶¶]Received rituximab concomitantly with rFVIIIFc.

[†††]This patient was first on rFVIIIFc ITI (83 IU/kg q.d.) for 15 weeks (titre=26 BU/mL), switched away to another factor ITI for 13 weeks and then restarted rFVIIIFc ITI on 29 March 2017 (titre=44 BU/mL) with rFVIIIFc 21 IU/kg per hour drip treatment regimen, and achieved negative inhibitor titre 13 weeks after restart of rFVIIIFc ITI and was tolerized after 32 weeks of treatment; patient is currently on rFVIIIFc prophylaxis.

[‡‡‡]This patient was enrolled with a historical peak inhibitor titre of 30.0 BU/mL. During the final data cleaning, the value was corrected to be 3.0 BU/mL instead.

[§§§]This patient transitioned to rFVIIIFc prophylaxis after 64 weeks of rFVIIIFc ITI treatment, laboratory assessments on normal recovery and time to half-life ≥6 hours were available 58 weeks after the patient transitioned to rFVIIIFc prophylaxis.

[¶¶¶]This patient was considered tolerized by the treating physician but showed a low-titre inhibitor during the follow-up period and remains on rFVIIIFc ITI at the time of data capture.

patients (23/29 [79%]) did not report any adherence issues. At the time of data capture, 21/29 patients (72%; 10/10 first-time, 11/19 rescue) were receiving rFVIIIFc (prophylaxis or ITI). One rescue patient received bypass agent prophylaxis in addition to rFVIIIFc ITI.

No adverse events were assessed as related to rFVIIIFc. In total, 19 surgeries were performed concomitant with ITI (eight [two major and six minor] in first-time and 11 [10 minor and one unclassified] in rescue patients). The two major surgeries were craniotomy and reconstruction of a left parietal defect in 2 patients. rFVIIIFc ITI was uninterrupted during all surgery and post-operative periods; bypass agent–controlled bleeding during all procedures among first-time patients and 7/11 procedures among rescue patients.

This retrospective chart review in a real-world setting shows that first-time ITI patients achieved rapid tolerization with a high success

Time (weeks)							
	From start of ITI to						
Inhibitor diagnosis to start of rFVIIIFc ITI	Negative Bethesda titre[§]	Normal recovery[¶]	Half-life ≥6 h[‡‡]	Tolerization[‡‡]	Duration of rFVIIIFc ITI	Current titre (BU/mL)	Current status
6	3	NR	3	3	3	Negative	rFVIIIFc prophylaxis
11	4	10	21	21	21	Negative	rFVIIIFc prophylaxis
18	9	NR	21	21	23	Negative	rFVIIIFc prophylaxis
12	**24**	NR	29	29	30	Negative	rFVIIIFc prophylaxis
41	**30**	56	NR	30	64	Negative	rFVIIIFc prophylaxis
1	**31**	NR	40	40	40	Negative	rFVIIIFc prophylaxis
0	**41**	NR	NR	59	71	Negative	rFVIIIFc prophylaxis
4	**64**	112	112	64	64	Negative	rFVIIIFc prophylaxis
1	**99**	N/A	N/A	99	157	1.3[¶¶¶]	rFVIIIFc ITI
6	N/A	N/A	N/A	N/A	59	4.4	rFVIIIFc ITI

TABLE 2 Rescue ITI patients[†, ‡]

Patient	FVIII genotype	Number of prior ITI regimens	Inhibitor titre (BU/mL)		Factor brand being used when inhibitor developed
			Historical peak (pre-ITI)	Immediately pre-rFVIIIFc ITI	
2-4[††]	Intron−22	1	**1178.0**	1.0	rFVIII (Advate, Baxalta US Inc, Lexington, MA)
2-1	Intron−22	7	**250.0**	9.0	rFVIII (Advate, Baxalta US Inc, Lexington, MA)
2-19[‡‡, ¶¶]	Intron−22	2	**224.0**	**15.0**	rFVIII (Advate, Baxalta US Inc, Lexington, MA)
2-9	Intron−22	3	11.0	1.3	rFVIII (Advate, Baxalta US Inc, Lexington, MA)
2-2	Intron−22	5	67.0	4.0	rFVIII (Advate, Baxalta US Inc, Lexington, MA)
2-7[‡‡]	Nonsense mutation	1	**306.0**	**129.0**	rFVIII (Advate, Baxalta US Inc, Lexington, MA)
2-5[‡‡,†††]	Intron−22	2	**460.0**	**200.0**	rFVIIIFc (Eloctate, Sanofi, Waltham, MA)
2-3	Partial gene deletion	3	100.0	**34.6**	rFVIII (Recombinate, Baxalta US Inc, Lexington, MA)
2-6	Intron−22	3	41.8	**22.3**	rFVIII (Advate, Baxalta US Inc, Lexington, MA)
2-10	Intron−22	2	8.0	0.6	rFVIII (Advate, Baxalta US Inc, Lexington, MA)
2-8	Inversion	1	43.7	**35.6**	rFVIII (Advate, Baxalta US Inc, Lexington, MA)
2-11	Large deletion	4	**1024.0**	**237.0**	rFVIII (Helixate, CSL Behring LLC, Kankakee, IL)
2-12	Nonsense mutation	4	**409.0**	**26.0**	rFVIII (Helixate, CSL Behring LLC, Kankakee, IL)
2-13[¶¶]	Insertion	6	18.0	1.9	rFVIII (Refacto, Wyeth, Philadelphia, PA)
2-14[¶¶]	Unknown	1	29.0	**27.2**	Missing data
2-15[¶¶]	Intron−22	2	24.0	4.1	rFVIII (Kogenate, Bayer HealthCare LLC, Whippany, NJ)
2-16[¶¶]	Unknown	1	110.0	**50.0**	rFVIII (Advate, Baxalta US Inc, Lexington, MA)
2-17[¶¶]	Small deletion	2	**410.0**	**99.2**	rFVIII (Kogenate FS, Bayer HealthCare LLC, Whippany, NJ)
2-18[¶¶]	Intron−22	3	**275.0**	1.0	rFVIII (Kogenate, Bayer HealthCare LLC, Whippany, NJ)

Abbreviations: BPA, bypass agent; BU, Bethesda unit; FVIII, factor VIII; ITI, immune tolerance induction; N/A, not applicable; q.3.d., every three days; q.d., once daily; q.o.d., every other day; rFVIIIFc, recombinant factor VIII Fc fusion protein; t.i.w., three times per week.

[†]Patients are sorted in ascending order according to time from the start of ITI to tolerization first and then to negative Bethesda titre. Patient numbers were randomly assigned.

[‡]Bolded data indicate high-risk features.

[§]Time to first negative inhibitor titre: time interval (in weeks) from the start date of ITI treatment with rFVIIIFc to date of the patient's first time reaching inhibitor titre of <0.6 BU/mL.

[¶]Time to tolerization: time interval (in weeks) from the start date of ITI treatment with rFVIIIFc to the date when the physician reported that this patient reached tolerization.

[††]This patient stopped traditional ITI after 21.7 weeks of rFVIIIFc ITI treatment and transitioned to enhanced rFVIIIFc prophylaxis.

[‡‡]Received rituximab concomitantly with rFVIIIFc.

[§§]This patient was tolerized after 47 weeks of rFVIIIFc ITI treatment and re-developed inhibitors approximately 10 weeks after tolerization.

[¶¶]Newly identified patient.

[†††]Patient reached negative Bethesda titre 13 weeks after the start of rFVIIIFc ITI; stopped rFVIIIFc ITI with BU=2, switched to another factor ITI and tolerized; now this patient is on rFVIIIFc prophylaxis (116 IU/kg q.o.d.).

rate (80%) using rFVIIIFc. Among rescue patients, more than half reached a negative titre within 21 weeks of starting rFVIIIFc ITI and 4 subsequently reached tolerization. This was achieved using various dosing regimens with lower factor usage than recommended to date for success in this high-risk group.[1]

The results demonstrate a shorter median time to tolerization with rFVIIIFc ITI than reported with other FVIII regimens[5] or with von Willebrand factor-containing plasma-derived FVIII.[6] Despite being at a higher risk of ITI failure and receiving half of the median factor dose (700 vs 1400 IU/kg/week) administered to patients in the high-dose arm of the International Immune Tolerance study,[5] this population took markedly less time to achieve tolerance than in that study.

Our results match previous observations that achieving successful tolerization in rescue ITI patients is generally difficult and much less likely to be successful, making the first attempt at ITI

		Time (weeks)					
			Start of ITI to				
rFVIIIFc ITI regimen	Weekly factor usage (IU/kg)	Inhibitor diagnosis to start of rFVIIIFc ITI	Negative Bethesda titre[§]	Tolerization[¶]	Duration of rFVIIIFc ITI	Current titre (BU/mL)	Current status
100 IU/kg q.o.d.	350	94	**13**	22	22	Negative	rFVIIIFc prophylaxis
200 IU/kg q.d.	1400	**297**	**28**	35	35	Negative	rFVIIIFc prophylaxis
100 IU/kg q.o.d.	350	**238**	**14**	47	80	0.9	rFVIIIFc ITI
100 IU/kg q.o.d.	350	**626**	**100**	101	135	Negative	rFVIIIFc prophylaxis
150 IU/kg q.d.	1050	**249**	3	N/A	41	7.0	Emicizumab
100 IU/kg q.d.	700	**243**	**13**	N/A	87	36.0	Emicizumab
150 IU/kg q.d.	1050	42	**13**	N/A	90	Negative	rFVIIIFc prophylaxis
191.5 IU/kg q.o.d.	670	**498**	**31**	N/A	82	14.6	rFVIIIFc ITI; BPA prophylaxis
130 IU/kg q.d.	910	**265**	**68**	N/A	169	2.4	Emicizumab
100 IU/kg q.3.d.	233	**439**	**70**	N/A	83	Negative	rFVIIIFc ITI
200 IU/kg q.o.d.	700	**271**	N/A	N/A	68	44.0	rFVIIIFc ITI
100 IU/kg q.d.	700	**473**	N/A	N/A	38	1024.0	rFVIIIFc ITI
100 IU/kg q.d.	700	**491**	N/A	N/A	94	166.0	BPA prophylaxis
130 IU/kg q.d.	910	**989**	N/A	N/A	47	5.0	Emicizumab
43 IU/kg t.i.w.	129	**2242**	N/A	N/A	70	2.5	rFVIIIFc ITI
52 IU/kg t.i.w.	156	**934**	N/A	N/A	33	40.6	BPA prophylaxis
186 IU/kg q.d.	1302	32	N/A	N/A	32	26.2	rFVIIIFc ITI
200 IU/kg q.d.	1400	**216**	N/A	N/A	11	72.0	Humate-P prophylaxis; BPA prophylaxis
100 IU/kg q.o.d.	350	**467**	N/A	N/A	24	34.8	Emicizumab

most important. Increasingly, as well, clinicians advocate for commencing ITI as soon as possible after high-titre inhibitor development.[1] Our analysis showed that, for the most part, clinicians involved in this North American real-world study started ITI (in first-time ITI patients) without waiting for inhibitor titres to drop to a predefined level. Supporting this approach, all first-time ITI patients initiating rFVIIIFc ITI within 1 month of inhibitor diagnosis were tolerized.

The high success rate among patients undergoing first-time ITI included in this chart review may be due partly to potential immunomodulatory properties of rFVIIIFc.[7] Further study of the immunogenicity of rFVIIIFc, in previously untreated patients with haemophilia A, is being analysed (ClinicalTrials.gov: NCT02234323).

Limitations of this study include its retrospective nature, small patient population and potential for reporting biases. The impact of

ITI initiation soon after inhibitor detection is not fully understood and may have contributed to the success of first-time ITI.[8] Additionally, the definition of tolerization applied in this study included attaining a 6-hour FVIII half-life. While this has been an accepted parameter for characterizing tolerization[5] in an era of extended half-life factors, new studies are required to determine the appropriate half-life target for defining success of ITI.

Although the haemophilia treatment landscape is changing with the advent of emicizumab as well as potentially other rebalancing therapies, all of which can be used in patients with inhibitors, eradication of inhibitors remains an important goal for patients with high-titre inhibitors and ITI continues to be the standard of care for these patients. However, current ITI regimens require frequent factor infusions and a long duration of treatment, and are only efficacious in 50%–70% of patients.[9] More effective regimens that establish Bethesda negativity and achieve successful ITI more quickly would likely reduce the substantial risk of bleeding during early ITI (this may be mitigated by concomitant administration of emicizumab during ITI), improve long-term patient outcomes and reduce treatment burden and improve patient quality of life.[9] Since ITI is typically costly, more effective and efficient tolerization could also reduce healthcare utilization and costs associated with ITI.[10]

In conclusion, extended half-life rFVIIIFc is an effective option for ITI therapy in patients with severe haemophilia A and inhibitors at high risk of ITI failure in a real-world setting. Prospective studies are underway assessing the efficacy of first-time and rescue rFVIIIFc ITI in patients with haemophilia A who have developed inhibitors (verITI-8 [NCT03093480]; reITIrate [NCT03103542]).

KEYWORDS

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

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CONFLICT OF INTEREST

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AUTHOR CONTRIBUTIONS

M. Carcao, E. Tsao, J. Feng, J. Dumont and N. Jain were responsible for the study concept and design. M. Carcao, A. Shapiro, N. Hwang, S. Pipe, S. Ahuja, K. Lieuw, J. Staber, M. Belletrutti, H. L. Sun, H. Ding, M. Wang, V. Price, M. Steele and Z. Al-Khateeb were responsible for data acquisition. All authors contributed to the interpretation of data, writing and revising the letter, as well as providing final approval of the version to be published.

DATA AVAILABILITY STATEMENT

Qualified researchers may request access to patient level data and related study documents including the clinical study report, study protocol with any amendments, blank case report form, statistical analysis plan and data set specifications. Patient level data will be anonymized and study documents will be redacted to protect the privacy of our trial participants. Further details on Sanofi's data sharing criteria, eligible studies, and process for requesting access can be found at: https://www.clinicalstudydatarequest.com/.

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