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ORIGINAL ARTICLE

Immune tolerance induction with moroctocog-alpha (Refacto/Refacto AF) in a population of Italian haemophilia A patients with high-titre inhibitors: Data from REF.IT Registry

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Abstract

Background: The appearance of inhibitors is the most serious complication in haemophilia A (HA) patients. The primary objective is their eradication. Up to date, immune tolerance induction (ITI) was the only therapeutic option to achieve this.

Aim: To assess the efficacy of moroctocog-alpha as an ITI regimen in a population of HA patients with high-titre inhibitors.

Methods: The REF.IT Registry is a retrospective-prospective study that collected data on all patients with HA and high-titre inhibitors treated with moroctocog-alpha as an ITI regimen at twelve Italian Haemophilia Centres.

Results: We enrolled 27 patients, 85.2% were children. All patients were high responders, 88.9% had severe HA. We found 69.3% of them had one or more risk factors for poor ITI prognosis, 14.8% were ITI rescue. Overall 59.3% achieved a complete/partial success (complete in 51.9%). ITI failed in 11 patients, 63.6% of them with poor-prognosis risk factors. Inhibitors appeared after a mean of 27 exposure days. Mean historical peak was 78.8 BU/mL. The primary ITIs started on average 20.2 months after the diagnosis. A partial or complete success after a mean of 15 months of treatment was achieved in 56.6% of the children while the same result was obtained by 75.0% adults after 22 months from ITI onset. Patients who were treated with high-dose moroctocog-alpha (200 UI/kg/day) were 63.0%.

Conclusion: Our Registry showed that the use of moroctocog-alpha in the setting of ITI was effective and safe also in a population of patients with high-titre inhibitors, presenting one or more risk factors for poor ITI prognosis.

KEYWORDS

haemophilia A with inhibitors, immune tolerance induction, moroctocog-alpha, poor-prognosis ITI patients

1 | BACKGROUND

Haemophilia A is a rare congenital disease caused by factor VIII (FVIII) deficiency that affects 1/5000-10 000 males. The severity of the disease depends on the plasmatic FVIII level, in cases of severe haemophilia (FVIII < 1%) spontaneous bleeding and frequent haemarthroses can cause disability, can reduce the quality of life, and in some cases (eg intracranial haemorrhages) can be life-threatening.[1] Prophylaxis with FVIII concentrate is mandatory for reducing bleeding risk,[2] but exposure to exogenous FVIII is associated with the risk of inhibitor development.[3] The appearance of allo-antibodies against FVIII is the most serious complication in haemophilia A patients. In fact, it was estimated that about 30% of subjects with severe disease of which 5% of them with mild or moderate haemophilia experienced inhibitor development.[4] Immune tolerance induction (ITI) is the standard care to eradicate the inhibitors. FVIII concentrate can be used at a high dose of 200 IU/kg/day, at a low dose of 50 IU/Kg/three times a week or at an intermediate- dose of 100-150 IU/Kg/day,[5-7] but no standard regimens have been defined. A review performed by Ettingshausen et al[8] showed that the different regimens can be successfully used in patients with a good prognosis, instead, the high-dose treatment is recommended in patients with risk factors for poor ITI prognosis. Usually first ITI was started with the same concentrate that caused inhibitor development, but this is not mandatory while it is still debatable, which replacement factor should be used in case of ITI rescue. The recent UK guidelines in cases of poor responder children propose the FVIII dose increase, the introduction of plasmaderived FVIII with a high vonWillebrand Factor content (pdFVIII/vWF) and/or immune suppression with rituximab as second-line therapy, while the use of recombinant FVIII (rFVIII) is recommended only in cases of primary ITI. No indications are given on its use in cases of ITI rescue.[9] Some published articles reported the use of rFVIII in patients with congenital haemophilia and inhibitors in cases of primary ITI[10,11] but no clear data are available on its use as second-line therapy. A recent case report showed the success of ITI rescue with rFVIII in a poor risk haemophiliac A inhibitor young child.[12] The rate of complete primary ITI success with rFVIII is estimated between 25% and 100%.[13] This very high variability is due to different definitions of ITI success, to different regimens of treatment and to the different characteristics of each patient. The risk of failure remains high especially in cases of patients presenting risk factors for poor ITI prognosis. Carcao et al[14] recently reported the use of efmoroctocog-alpha (rFVIII-Fc), an extended half-life (EHL) recombinant FVIII, in the treatment of 19 patients (7 first ITI, and 12 rescue ITI) with haemophilia A and inhibitors. Toleration was initially achieved in overall 57.9% of patients, but final outcomes were not available. Almost, all enrolled subjects had at least one high-risk feature for ITI failure. Similar data were reported by Kreuz et al[15] in the ObsITI study in which the 62.9% of high responder patients with ≥1 poor-prognosis factor achieved a complete success. Below, we report the data from the'REFACTO® for ITI' (the REF.IT Registry).

2 | AIM

The primary end-point of this Registry was to assess the efficacy of moroctocog-alpha as ITI regimen (primary or rescue) in a population of patients with haemophilia A and high-titre inhibitors (≥5 BU/mL).

The secondary end-points were to assess the difference between patients with or without risk factors for poor ITI prognosis in terms of complete or partial success, and to assess the difference among three dose regimens of treatment (high, intermediate or low).

3 | PATIENTS AND METHODS

3.1 | Patients

The 'REFACTO® for ITI' (the REF.IT Registry) is a retrospective-prospective study that collected data on all patients with haemophilia A and high-titre inhibitors (≥5 BU/mL), treated with moroctocog-alpha as an ITI regimen from 12 Italian Haemophilia Centres. Data collection started in January 2016 and enrolled all eligible subjects from the previous ten years (retrospective phase) and up to the end of December 2017 for the prospective one. The participating Centres confirmed that all patients treated with morocotocog-alfa as an ITI regimen primary or rescue were included in this Registry, and there were no exclusions.

The study protocol was approved by each institution's Ethical Committee and was conducted in accordance with the principles of the Declaration of Helsinki and with local laws and regulations. All patients provided written informed consent. In the case of patients <18 years of age the informed consent was signed by their parents.

Statistical analyses were performed in a total of 27 patients. We considered paediatric patients all subjects ≤12 years of age.

3.2 | Methods

All patients were assessed for (a) demographic and baseline characteristics such as age, age at diagnosis and clinical conditions (eg viral infections); (b) descriptive characteristics of haemophilia: type, degree, familiarity and genetics; (c) descriptive characteristics of inhibitor development and management; (d) descriptive characteristics of immune tolerance induction with moroctocog-alpha; (e) success of ITI (complete, partial or failure); and (f) adverse events (AE; (g) outcomes.

Following the international guidelines the success of ITI was defined as:

- Complete: absence of inhibitor (<0.6 BU/mL), this cut-off was chosen by all the participating centres since there was no central laboratory collection; FVIII recovery >66%; FVIII half-life >6 hours
- Partial: if after 33 months of ITI the inhibitor was absent, but persistently altered recovery and half-life of FVIII
- Failure: no reduction of inhibitor titre by at least 20% for each 6-month therapy period after the first three; or failure to achieve complete or partial tolerance after 33 months of ITI; or interruption of the study before reaching tolerance for any reason.

- Relapse: inhibitor reappearance during the 12 months of follow-up in the course of prophylaxis after the tolerance had been reached, was evaluated as a double confirmation of the positivity of the Bethesda test, and as a reduction in the recovery of FVIII or half-life.
- Rescue: a new ITI performed with another concentrate after the failure of a primary ITI.
- Risk factors for poor ITI prognosis: rescue ITI; age ≥7 years; historical inhibitor peak ≥200 BU; more than 2 years since inhibitor diagnosis and ITI start; inhibitor titre ≥10 BU at the start of ITI with moroctocog-alpha

3.3 | ITI regimens

Both ITI, primary or rescue, were considered in this Registry. All treatment regimens were included: low-dose ITI (50 IU/Kg three times a week), intermediate-dose ITI (100-150 IU/Kg/day) and high-dose ITI (200 IU/Kg/day).

3.4 | Statistical analysis

Descriptive statistical analyses were performed using SAS statistical software version 9.2 (SAS) in Windows 7 professional environment. Due to the non-interventional nature of this study, all the patients were included in the analysis and no particular statistical strategy was adopted. All the variables collected were summarized by appropriate descriptive statistics: mean, standard deviation (SD), range and/or percentage.

Due to the small sample of patients, all the comparative statistics between different groups were performed with Fisher's Exact Text ($P < .05$). AEs were coded using the MedDRA (Medical Dictionary for Regulatory Activities).

4 | RESULTS

In our Registry, we enrolled 27 patients. Twenty-one of them were enrolled in the retrospective phase (10 years), while the remaining six were enrolled in the prospective one (2 years). Statistical analysis included all the data on 27 enrolled patients (23 paediatrics and 4 adults), collected from 12 Hemophilia Centers in Italy. The characteristics of patients are reported in Table 1.

4.1 | Paediatric patients

At the inhibitor diagnosis, the 23 patients in this Registry were paediatrics (mean age 25.5 ± 12.4 months), who developed a high-titre inhibitor after a median of 12.0 ± 8.9 ED. They presented a

TABLE 1 Patient characteristics

	Total (=27 patients)	Paediatrics (=23 patients)	Adults (=4 patients)
No. haemophilia degree (%)			
Severe	23 (85.2)	21 (91.3)	2 (50.0)
Moderate	3 (11.1)	2 (8.7)	1 (25.0)
Mild	1 (3.7)	0 (0.0)	1 (25.0)
Ethnicity (%):			
White/Caucasian	26 (96.3)	22 (95.7)	4 (100.0)
Black/African-American	1 (3.7)	1 (4.3)	0 (0.0)
Genetic mutations (%):			
Int22Inv	16 (59.3)	16 (69.6)	0 (0.0)
Small Ins	3 (11.1)	3 (13.0)	0 (0.0)
Small Del	1 (3.7)	1 (4.4)	0 (0.0)
Missense	3 (11.1)	1 (4.4)	2 (50.0)
Nonsense	1 (3.7)	1 (4.4)	0 (0.0)
Splicing	1 (3.7)	1 (4.4)	0 (0.0)
Not available	2 (7.4)	0 (0.0)	2 (50.0)
No. Family history for HA (%)	14 (51.9)	13 (56.5)	1 (25.0)
No. Family history for INH (%)	4 (14.8)	4 (17.4)	0 (0.0)
Inhibitors:			
After ED (Median days ± SD)	16.5 ± 34.9	12.0 ± 8.9	77.5 ± 58.8
Historical peak (Median BU/mL ± SD)	32.0 ± 117.1	36.0 ± 124.5	21.0 ± 60.3
Pre-ITI titre (Median BU/mL ± SD)	6.0 ± 18.4	6.0 ± 19.7	7.0 ± 6.2

Abbreviations: ED, exposure days; HA, haemophilia A; INH, inhibitors; Int22Inv, Intron 22 Inversion; ITI, immune tolerance induction; SD, standard deviation.

TABLE 2 Number of risk factors for poor-prognosis ITI, type and regimen of ITI, type of success and time to achieve complete or partial success in the paediatric patients

Patient ID	Risk factors for poor ITI (n)	Type of ITI	Dose regimen	Type of success	Time to CS or RP (months)
01	1	P	H	CS	6
02	1	P	H	CS	6
03	0	P	H	F	NA
04	0	P	H	F	NA
05	0	P	H	CS	17
06	1	P	I	F	NA
07	2	P	H	F	NA
08	0	P	H	F	NA
09	0	P	H	CS	24
10	0	P	L	F	NA
11	0	P	L	CS	23
12	1	P	H	CS	3
13	3	P	I	PS	4
14	2	R	H	CS	29
15	1	R	H	PS	19
16	0	P	H	CS	20
17	0	P	H	CS	1
18	5	P	I	F	NA
19	1	R	H	F	NA
20	2	P	I	F	NA
21	1	P	H	PS	21
22	0	P	I	CS	24
23	3	P	H	F	NA

Note: Risk factors for poor-prognosis ITI: rescue ITI; age ≥7 years; historical inhibitor peak ≥200 BU/mL; over 2 y since inhibitor diagnosis; inhibitor titre ≥10 BU at the start of ITI with moroctocog-alpha.
Abbreviations: CS, complete success; F, failure; H, high-dose regimen (200 IU/Kg/day); I, intermediate-dose regimen (100-150 IU/Kg/day); ITI, immune tolerance induction; L, low-dose regimen (50 IU/Kg/three times a week); NA, not achieved; P, Primary ITI; PS, partial success; R, rescue ITI.

mean historical peak of 36.0 BU/mL (range 5.6-500.0). An ITI with moroctocog-alpha was started on average 22.4 ± 23.0 months after the diagnosis of the inhibitor, with a median inhibitor titre of 6.0 ± 19.7 BU/mL. ITI was primary in the 87.0% of cases. Median peak inhibitor titre during ITI was 205.5 BU/mL (range 2.1-5000.0). A high-dose regimen at 200 IU/Kg/day was applied to 69.6% of patients, while the intermediate-dose regimen at 100-150 IU/Kg/day to 21.7%, and the low-dose regimen 50.0 IU/Kg/three times a week to the remaining 8.7%. Complete or partial success was achieved in overall 56.6% (complete 43.5%) of children after a median of 18.5 months of treatment; while in the case of three ITI rescues, one of which obtained a complete success after 29 months; the second obtained a partial success after 16 months, and the third was declared failed after 7 months, as the patient maintained an inhibitor titre of 392 BU/mL. The two children with moderate haemophilia obtained respectively a complete success after three months and a partial success. At least one risk factor for poor ITI prognosis (range 1-5) was found in 13/23 patients. Number of risk factors for poor ITI prognosis, success and time to success are detailed in Table 2.

Complete success was obtained in 6/16 (37.5%) patients who presented with intron 22 inversion and in 5/7 (71.5%) patients with other mutations. Failure was reported in 9/16 subjects (56.2%) with intron 22 inversion, while the same result was obtained in 1/7 (14.3%) with other mutations. A comparison between the success in the patients presenting intron 22 inversion and those presenting other mutations was statistically not significant (P = .1486).

One or more bleeding episodes were experienced in 60.9% of patients all treated on demand with recombinant factor VII activated (rFVIIa). Among these, two were ileo-psoas haemorrhages.

Nine children, who had a complete success, were subsequently put on prophylaxis with moroctocog-alpha every other day (five patients) or three times a week (four patients) at a mean dosage of 50 IU/kg. Eight patients in which the ITI failed were subsequently treated on demand with recombinant FVII activated (rFVIIa). A rescue ITI with plasmaderived FVIII was started in one child after ITI failure. No data are available for the remaining patients.

4.2 | Adult patients

At diagnosis the four adult patients included in this Registry had a mean of 30.8 ± 13.6 years of age, developed a high-titre inhibitor after a median of 77.5 ED (range 17.0-150.0) and presented a median historical peak of 21.0 BU/mL (range 6.0-134.4). An ITI with moroctocog-alpha was started on average 29.7 months after the diagnosis of inhibitor, with a median inhibitor titre of 7.0 BU/mL. ITI was rescue in half of the cases. High-dose regimen at 200 IU/Kg/day was applied to one patient undergoing rescue ITI, while the intermediate-dose regimen at 100-150 IU/Kg/day to another patient undergoing primary ITI and the low-dose regimen 25.0 IU/Kg/three times a week to the remaining two patients equally divided between rescue and primary ITI. Median peak inhibitor titre during ITI was 67.0 BU/mL (range 7.0-130.0). Complete success was obtained by 75.0% of adults after 22.0 months from ITI onset, two had severe haemophilia, while one was a mild subject. In the remaining moderate patient, the ITI rescue as stopped after 15 months from onset, due to the permanence of a high-titre inhibitor. All patients presented risk factors for poor ITI prognosis (range 1-4). Two patients were HCV+, while no patients had HIV infection. No patients experienced severe haemorrhagic events during ITI. Two adult patients, who had a complete success, presented a missense mutation, while for the remaining the genetic data were missing.

The patients, who experienced a complete success, were initially put on prophylaxis with moroctocog-alpha every other day and subsequently three times a week. No data are available about the used dosage. However, a second ITI rescue with another concentrate was tried in the patient, in which the ITI with moroctocog-alpha failed.

4.3 | Overall

Complete success was obtained in the 51.9% of patients, while the sum of complete or partial success reached 59.3%. Among the patients who achieved a complete or a partial success 62.5% presented one or more risk factors for poor ITI prognosis, the different success among patients with or without risk factors for poor ITI prognosis is shown in Table 3.

Complete or partial successes were achieved in 58.8% of patients treated with a high-dose regimen, while the same result was achieved in 60% of patients treated with low- or intermediate-dose regimens. No significant differences were reported on the regimen choice based on the number of risk factors for poor ITI prognosis. No adverse events due to treatment with moroctocog-alpha were reported in this Registry. Complete or partial successes were achieved in 56.5% of primary ITI and in 60% of rescue ITI, no statistical significant difference was found between first- and second-line treatment. Different successes among adult or paediatric patients are reported in Table 4.

In the case of patients who reached a complete or a partial success, the mean time elapsed from ITI start and inhibitor negative was respectively: 11 months (range 1-53) for total cohort; 8 months (range 1-25) for paediatrics and 20 months (range 3-53) for adults. The eight patients enrolled during the prospective phase negativized the inhibitor in a shorter time, mean 3 months (range 1-4).

5 | DISCUSSION

Our REF.IT study showed a complete or partial success of 59% in the FVIII inhibitor eradication in a cohort of patients with high-titre inhibitors of which 63% of cases presented one or more risk factors for poor ITI prognosis.

Three different treatment regimens are now used to obtain tolerization in patients presenting allo-antibodies against FVIII: the Bonn protocol,[16] the Van Creveld protocol[17] and the Malmö protocol.[18] However clinicians often adopt several changes regarding these regimens.

The main risk factors for ITI prognosis were universally recognized: the historical peak of FVIII inhibitor titre (cut-off 200 BU/mL), the inhibitor titre before the ITI start (cut-off 10 BU/mL), the inhibitor peak during ITI and the age of patients ≥7 years, over 2 years since inhibitor diagnosis and the ITI start. In addition, the non-null FVIII mutations such as small insertion or deletions and missense mutations were associated with a good outcome.[19,20]

Previous reported studies enrolled patients without poor ITI prognosis risk factors treated with different FVIII concentrates. The International ITI study[19] collected data for 115 'good-risk' patients randomized to high- or low-dose treatment, failure occurred in the 25.8%. Complete or partial success did not differ between two treatment arms, data similar to our Registry. Usually, the primary

TABLE 3 Different success rates among patients with or without risk factors for poor-prognosis ITI

ITI success	Overall patients (=27)	Good- prognosis ITI patients (=10)	Poor- prognosis ITI patients (=17)
CS and PS (%)	16 (59.3)	6 (60.0)	10 (58.8)
Failure (%)	11(40.7)	4 (40.0)	7(41.2)
P value (<.05)	ns	ns	ns

Note: Risk factors for poor-prognosis ITI: rescue ITI; age ≥7 years; historical inhibitor peak ≥200 BU/mL; over 2 y since inhibitor diagnosis; inhibitor titre ≥10 BU at the start of ITI with moroctocog-alpha. Good-prognosis ITI: patients without risk factors.
Abbreviations: CS, complete success; ITI, immune tolerance induction; Ns, not significant; PS, partial success.

TABLE 4 Different success rate among adult and paediatric patients in cases of primary or rescue immune tolerance induction

Immune tolerance induction success	Overall patients (=27)	Adult patients (=4)	Paediatric patients (=23)
Complete Success No. (%)	14 (51.9)	3 (75.0)	11 (47.8)
Primary ITI	11 (40.8)	2 (50.0)	9 (39.1)
Rescue	3 (11.1)	1 (25.0)	2 (8.7)
Partial Succes No. (%)	2 (7.4)	0 (0.0)	2 (8.7)
Primary ITI	2 (7.4)	0 (0.0)	2 (8.7)
Rescue	0 (0.0)	0 (0.0)	0 (0.0)
Failure No. (%)	11 (40.7)	1 (25.0)	10 (43.5)
Primary ITI	9 (33.3)	0 (0.0)	9 (39.1)
Rescue	2 (7.4)	1 (25.0)	1 (4.4)

ITI was performed with the same concentrate, which developed the inhibitors, but it is still debatable, which replacement factor should be used in cases of an ITI rescue. The recent UK guidelines suggest a FVIII dose increase, the introduction of plasmaderived FVIII with a high vonWillebrand Factor content (pdFVIII/vWF) and/or immunosuppression with rituximab as second-line therapy in case of children with poor ITI prognosis. However, use of rFVIII is recommended only in cases of primary ITI, but no indications are given on its use in rescue ITI cases.[9] These facts are supported by different published cases[10,11] on the use of rFVIII for primary ITI for eradicating the inhibitors in patients with congenital haemophilia, conversely as reported by Zanon et al,[12] in which a poor-prognosis child who had full treatment with a rFVIII during his ITI rescue. In this study, the use of recombinant FVIII, moroctocog-alpha, for the immune tolerance induction in a population of patients presenting high-titre inhibitors was proven to be effective in an overall 59.3% of subjects. A complete success was reached in 51.9%, while a partial or complete success was obtained in 60% of rescue ITI's, data similar to that reported by the ObsITI Study.[15] Also in this case, almost all patients had a high inhibitor titre, but the ITI was performed with a single pdFVIII/vWF; no large studies were available for ITI with single rFVIII, unlike the REF.IT study. In fact, our study is one of the largest in number of cases of patients treated during ITI with a single rFVIII concentrate.

Astermark et al[21] performed a review in which they evaluated the published studies and registries on ITI treatments and outcomes. Ten studies were considered, a total of 188 patients who underwent an ITI, in almost all cases with plasmaderived FVIII, some enriched with von Willebrand factor. High-titre inhibitors were found in 82.4%, but no data on risk factors for good or poor ITI prognosis were available. Only in one study,[22] all 11 paediatric patients were treated with a single rFVIII (octocog-alpha), while in the other studies rFVIII was adopted in a variable percentage of patients. In all these studies, the success rate was very high, between 62% and 91%. Data not confirmed in the international registries in which the complete or partial successes were respectively between 50.9% and 78.6% and 6% and 8.7%, more similar to our results.

Our Registry then confirmed the data shown by other registries, but the difference was represented by use of single rFVIII in a population of only high responder patients in which the risk factors for ITI prognosis were evaluated. Usually in ITI patients, the FVIII is administered every day; in paediatrics, a CVC must be inserted in order to carry out the infusion. The duration of ITI may last for up to 33 months. To improve the patient's quality of life, particularly the paediatric ones it would be recommendable to individualize the most appropiate FVIII in order to reach the best result.

The availability of different vials of recombinant concentrates (500 UI, 1000 UI, 2000 UI and 3000 UI) associated with a low volume of reconstitution of the drug makes the administration easier and more rapid reducing discomfort for the patient. It is advisable to bear in mind that the majority of patients are administered 200 UI/kg/die of FVIII during ITI. In the North American Immune Tolerance Registry—NAITR[23] several predictors for ITI outcomes were considered, but no statistical analyses were performed to correlate each single patient to the presence of risk factors for ITI prognosis and ITI outcome.

Carcao et al[14] reported the partial data on use of an EHL product for ITI, and the recent article published by Ljung et al[24] considers the new therapeutic strategies to eradicate the inhibitors in patients that failed one or more ITI's. Emicizumab, a subcutaneous bispecific monoclonal antibody, has recently been authorized for treating haemophilia A patients with and without inhibitors,[25,26] while other subcutaneous drugs are still under development. In the future, an alternative treatment may be represented by recombinant porcine FVIII, now allowed in cases of patients affected by acquired haemophilia A.[27] Also in the era of subcutaneous treatment without FVIII concentrates, as emicizumab, the eradication of inhibitors is fundamental to guarantee an easier and safer patient management in the event of surgery or bleeding. A gold standard to treat these patients remains the ITI, but given that the patients will most likely accept to undergo a single ITI, in future, it will be essential to choose the concentrate that gives the best chance of success immediately. Moroctocog-alpha which has demonstrated good therapeutic efficacy may be considered for this aim.

As recently reported by Le Quellec et al,[28] in the near future, another therapeutic option may be given by the concomitant use of emicizumab in the context of low-dose ITI with moroctocog-alpha or other FVIII concentrates, but further consistent data are needed to validate this new promising purpose.

6 | LIMITATIONS

Although our study is the only one reporting the results of ITI performed exclusively with moroctocog-alpha, the number of treated cases is not very high, especially concerning ITI rescue. Usually, the primary ITI is carried out with the FVIII concentrate that caused inhibitor development, therefore, finding many patients treated with a single concentrate becomes very difficult; since the international guidelines recommend performing second-line treatments with plasmaderived products. To date in the literature, there are only a few rescue ITI's conducted with a rFVIII.

7 | CONCLUSION

The conclusive analysis of our REF.IT Registry has shown that a treatment with moroctocog-alpha resulted effective in achieving immune tolerance also in a population of patients with high-titre inhibitors and presenting one or more risk factors for poor ITI prognosis. This recombinant FVIII was proven to be as effective as the plasma-derived products in eradicating inhibitors both in primary and rescue ITI, and at this moment, it may be an interesting therapeutic option for immune tolerance induction, even though more cases would be required to confirm these results. Given the good results obtained in our Registry, the morocotocog-alpha will be considered in the future for its use in association with other agents, such as emicizumab, in the management of patients with haemophilia A and inhibitors difficult to treat with the customary ITI regimens.

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EZ designed the study analyzed the data and corrected the paper, SP wrote the paper and analyzed the data, all other authors have given final approval of the version to be published. This study was performed with the unconditional support by Pfizer.

DISCLOSURES

All authors have read and understood HAEMOPHILIA policy on declaration of interests and declare that they have no competing interests.

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