

MEETING REPORT

The North American immune tolerance registry: contributions to the thirty-year experience with immune tolerance therapy

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Summary. The North American Immune Tolerance Registry (NAITR) began in 1992 as a project of the ISTH Factor VIII/IX Subcommittee with the goal of further determining immune tolerance induction (ITI) practices in Canada and the United States. This retrospective registry study, published in 2002, was limited in its capacity to provide definitive answers to many unresolved ITI practice issues. Nonetheless, it played a role in developing guidelines for current ITI practice and in generating hypotheses that must now be examined through rigorous prospective data collection efforts. For haemophilia A, the logical next step has been the initiation of international prospective randomized studies of ITI outcome relative to factor VIII (FVIII) dose and purity for subjects with high titre inhibitors. Both trials will additionally provide platforms for translational

study of the immunology of tolerance, a prelude to the next generation of safe and effective tolerizing strategies. For the less common problem of FIX inhibitor eradication, prospective randomized studies will not be a feasible way to confirm the NAITR observations. Coordinated international efforts will still be required to prospectively collect data on ITI outcome to document new potentially effective therapeutic strategies for inhibitor eradication. These registries will hopefully also serve to identify potential subjects for scientific studies of immunology of haemophilia B-related allergic phenomena, a devastating complication of FIX antibody development.

Keywords: haemophilia A, haemophilia B, immune tolerance, inhibitors

Introduction

The cumulative prevalence of inhibitor development in individuals with severe or moderately severe haemophilia A has been estimated to be as high as 33% [1]. Inhibitor incidence has not been as well documented amongst individuals with haemophilia B, but appears to be less frequent at 1–6% [2]. Treatment options for haemophilia patients with inhibitors are limited in number, useful in the acute management of bleeding, but less than satisfactory in providing a good long-term outcome for this population. Consequently, morbidity and mortality from

the haemorrhagic complications of haemophilia remain high, although not clearly defined [3]. Inhibitor eradication with immune tolerance induction (ITI) currently remains the best long-term option, particularly for high-titre antibodies. Since Professor Brackmann's first observation of its efficacy in haemophilia A (Fig. 1) [4], small groups of patients were treated with multiple high- and low-dose factor regimens, with and without concomitant immune modulation (IM) therapy [5–16]. Despite similar overall success, the time to induction of immune tolerance differed significantly amongst regimens [5–16]. Given the low incidence of Factor IX (FIX) inhibitors, experience with ITI in haemophilia B was limited [5,14,17].

Because of the treatment intensity, long-term expense and complications associated with ITI, particularly in paediatric populations, therapeutic optimization has always been a priority. To that end,

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Successful treatment of haemophilia A inhibitor patients with an induced immunotolerance

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Fig. 1. Title page from the manuscript presented in 1984 by Professor Brackmann at Fourth International Symposium on haemophilia treatment in Tokyo detailing his early experience with immune tolerance therapy.

a greater understanding of existing ITI practices, outcomes and outcome predictors was essential. The initial report from the International Immune Tolerance Registry provided first such aggregate data for haemophilia A [18]. A subsequent multivariate analysis of the international data set corroborated the initial significant outcome predictors of pre-induction titres ≤ 10 BU and high Factor VIII (FVIII) dosing regimens of at least $200 \text{ U kg}^{-1} \text{ day}^{-1}$ [19,20]. Age, peak historical titre and interval ≤ 5 years between diagnosis and therapy were significant outcome predictors only in a univariate analysis [19].

The North American Immune Tolerance Registry (NAITR) began in 1992 as a project of the ISTH Factor VIII/IX Subcommittee with the goal of further determining immune tolerance practices in Canada and the United States with respect to the identification of (i) therapeutic regimens in use; (ii) therapeutic outcomes; (iii) potential predictors of successful outcome and (iv) complications of therapy. The outcome of that study was published in 2002 and will serve as a reference for study methodology and results [21]. This paper will focus on a discussion of the some of the outcome predictors identified by the study and how these data have influenced our 30-year history with this therapeutic modality and current standards of practice.

Results

Inhibitor demographics/prevalence of ITI for haemophilia A and B

Amongst the haemophilia treatment centres included in the survey, 40% submitted data to the NAITR. The data represented 5000 (43%) of the then estimated North Americans with haemophilia A and 1325 (39%) with haemophilia B [22,23]. A past or current history of an inhibitor was reported in 486 (9.7%) haemophilia A patients and 32 (2.4%) haemophilia B patients. Overall, 91% of the FVIII

antibodies and 94% of FIX inhibitors occurred in subjects with severe disease (defined as factor activity $< 0.01 \text{ U mL}^{-1}$). Sixty-seven percent (326/486) of the FVIII inhibitors and 59% (19/32) of the FIX antibodies were high responders (HR) (historical titre of ≥ 5 BU).

Thirty-six percent (188/518) of all haemophilia A (171) and B (17) inhibitor subjects had undergone or were undergoing ITI at the time of the survey. Of these, 79% began in or after 1990, suggesting that the NAITR captured regional trends in ITI practice that were adapted from the earlier published European experience. Demographic data for both haemophilia A and B NAITR subjects can be found in Table 1 [21].

Definitions of ITI success and failure

The criteria for defining success (and failure) were established at each participating centre. The definition for haemophilia A and B cases included a negative inhibitor titre (≤ 1 BU) for 104 (87%); a normal factor recovery ($\geq 70\%$ of predicted) for 69 (56%); a normal factor half-life (≥ 12 h) for 34 (28%); and conversion from high to low responder

Table 1. Demographics of NAITR subjects with haemophilia A and B who completed immune tolerance induction (ITI) therapy.

Diagnosis	Haemophilia A (n = 164)	Haemophilia B (n = 16)
Severe haemophilia (%)	150 (93)	14 (88)
High responding inhibitors (%)	128 (78)	13 (81)
Family history of inhibitor (%)	31 (22)	5 (31)
Race		
Caucasian	100 (63)	8 (50)
African-American	21 (13)	4 (25)
Latino	24 (15)	2 (13)
Other	15 (9)	2 (12)
Mean (range) age (years) at ITI initiation	9.3 (0.1–64)	5.6 (0.8–19.6)

for 12 (10%) subjects. Only 30 (25%) registry subjects were determined to be successfully tolerised on the basis of a negative inhibitor titre as well as both a normal recovery and factor half-life [21]. The most common reasons for ITI failures were (i) a late rise in inhibitor titre after an initial decline whilst on ITI; (ii) patient/family desire to terminate ITI and (iii) central venous access device complications [21].

Haemophilia A

Therapeutic regimens in use. Although 47% of haemophilia A ITI subjects developed an inhibitor on ultra high purity products (monoclonal and recombinant), 75% of the cohort received these products as part of their tolerizing regimen. With respect to dosing regimen, 52% of the haemophilia A cohort were treated with FVIII at doses of ≥ 100 U Kg⁻¹ day⁻¹; only 14% received ≥ 200 U Kg⁻¹ day⁻¹. Non-daily dosing regimens (received by 91% of subjects in the <50 U Kg⁻¹ day⁻¹ category) were used in 21% of all haemophilia A ITI courses. Adjunctive IM therapy was used in 65 (40%) of all treatment courses, more frequently (58%) with regimens of ≥ 100 U FVIII per kg per day. Only 4/171 (2.3%) subjects received the complete or modified Malmö regimen as a component of immune tolerance. Finally, subjects who completed ITI received a mean of 16.8 (0–89) months of therapy initiated at a mean of 56 months (1–225) following inhibitor diagnosis [21].

Outcome data. Of the 164 haemophilia A subjects who completed ITI, 115 (70%) successfully achieved tolerance according to established institutional criteria. For HR haemophilia A subjects, 81/128 (63%) were successfully tolerised [21].

Outcome predictors. Several parameters were examined as possible ITI outcome predictors in HR haemophilia A inhibitor subjects. Although trends toward a younger mean age and a shorter mean interval between inhibitor diagnosis and ITI induction were noted in the successful group (9.7 years; 55 months) when compared with those who failed tolerance (10.6 years; 65 months), those differences were not statistically significant ($P = 0.6$ and 0.4 respectively). Furthermore, positive HIV serology (19% vs. 20%) and mean duration of ITI (15.6 months vs. 18.8 months) were not statistically different between the success and failure groups [21].

The rate of successful tolerance induction in African-Americans was compared with that for primarily Caucasian haemophilia A subjects and

noted to be lower in African-Americans, particularly amongst HRs. However, because of the small number of African-American subjects in the registry, outcome disparity did not achieve statistical significance [21].

Factor VIII product purity had no impact on ITI success in this cohort. The success rate amongst those subjects tolerised with intermediate or high purity products was 67.5% and not statistically different from either patients tolerised with monoclonal or recombinant factor (71%) or the overall success rate in the haemophilia A inhibitor group as a whole (70%) [21]. Other non-significant outcome parameters included the frequency of adverse events on therapy and central access complications during tolerance induction [21].

The influence of historical peak titre prior to ITI, peak inhibitor titre on immune tolerance and the pre-ITI induction titre on outcome in HR subjects was assessed. All three parameters were statistically significant predictors of outcome in univariate analyses. However, in a multivariate analysis, both the pre-ITI induction titre ($P = 0.001$) and peak titre on ITI ($P = 0.005$) were the most significant predictors of successful tolerance. Table 2 depicts the ITI success rate in HR severe haemophilia A subjects with pre-induction titres of <10 BU as significantly higher (83%) than in those with starting inhibitor levels of ≥ 10 BU (40%) ($P = 0.001$). As also noted in Table 2, the mean time to successful ITI was significantly shorter (14.4 months vs. 21.7 months, $P = 0.02$) when the starting titre was <10 BU. Of note, all 22 HRs with pre-ITI titres of <2 BU achieved ITI success within a mean 7.1 months of treatment [21].

The impact of dosing regimen on ITI success in haemophilia A was also evaluated. As shown in Table 3, no trend toward higher ITI success rates with increasing daily doses of FVIII was observed in the haemophilia A cohort as a whole. Conversely, there was a statistically significant inverse association between total daily dose and success in this cohort ($P = 0.03$), with the highest overall success rates

Table 2. NAITR: pre-induction titre as an outcome predictor of immune tolerance induction (ITI) success in severe high responder (HR) haemophilia A cohort.

	All HR	<10 BU*	≥ 10 BU	(P)
Overall success rate	63%	83%	40%	0.001
Mean time to success (months)	16.3	14.4	21.7	0.02

*All 22 HR haemophilia A subjects with pre-ITI titre <2 BU achieved success within a mean treatment time of 7.1 months.

Table 3. NAITR: influence of dosing regimen on immune tolerance induction (ITI) outcome in subjects with haemophilia A.

Dose (U Kg ⁻¹ day ⁻¹)	≥200	100–199	50–99	<50	P
All haemophilia A subjects					
Success (%)	41	74	72	83	0.03
Months to Success	11	8.5	8	13	<i>ns</i>
High responder haemophilia A with pre-ITI <10 BU					
Success (%)	–	84	78	100	<i>ns</i>
Months to Success	–	6.4	6.5	18.8	0.007

(83%) observed in the lowest daily FVIII dose category of <50 U Kg⁻¹ day⁻¹. The lowest success rate (41%) was observed in the smallest group that received ≥200 U Kg⁻¹ day⁻¹. As also shown in Table 3, there was not a significant difference amongst dosing categories with respect to median time to successful ITI. The adjunctive use of IM had no impact on either the rate of or time to successful ITI within each dose category (data not shown) [21].

The impact of the therapeutic regimen on successful ITI was further examined in the subset of HR haemophilia A subjects whose ITI had been initiated at inhibitor titres <10 BU. This subanalysis left too few evaluable subjects in the highest daily dosing category of ≥200 U Kg⁻¹ day⁻¹. As seen in Table 3, no statistically significant difference in the overall ITI success rate with increasing daily dose was observed. However, subjects who received at least 50 U Kg⁻¹ day⁻¹ with or without IM, achieved tolerance significantly faster (mean 6.5 months) when compared with those infused with less than 50 U Kg⁻¹ day⁻¹ (mean of 18.8 months) ($P = 0.007$) [21].

Maintenance of tolerance. In an earlier analysis of 93 haemophilia A subjects who successfully achieved immune tolerance, 75 (81%) were maintained on prophylactic FVIII infusion regimen for a variable period of time post-ITI induction [24]. The median dose used for maintenance therapy was 150 U kg per week (range: 17–700). Forty-eight (64%) subjects remained tolerant whilst on prophylactic FVIII infusions during a median observation period of 13 months (range: 0–129). Of the 27 subjects who were no longer receiving regular FVIII infusions, 17 (68%) remained tolerant over a median observation period of 19 months (range: 1–54); 9 had relapsed; and 1 had been lost to follow-up. Amongst the relapses, three occurred between 1 and 8 months after routine FVIII infusions were stopped and six were noted in subjects who had been maintained on FVIII therapy for a median time of 11 months (range: 2–61). Because of the questionnaire design, no outcome data was obtained on the 18/93 subjects

who were never placed on a FVIII regimen after successful tolerance was induced [24].

The definition of tolerance was reviewed for those nine subjects who relapsed whilst being maintained on a FVIII regimen. Tolerance had been defined by a normal recovery and survival in only 1/9 patients and by a normal recovery alone in 4/9 patients. Three relapsed subjects were determined to be tolerant solely on the basis of a negative Bethesda titre, and one success had been initially defined as a conversion from high to low responder status. The most stringent definition of success (normal recovery and survival) was under-represented (11% vs. 31%) and conversion to low responder status was over-represented (11% vs. 4%) in the relapse cohort when compared with the entire group of subjects who achieved successful tolerance. However, given the small number of relapsed subjects, no significant inverse correlation between the definition of success and the maintenance of successful tolerance could be definitive. [24].

NAITR contributions to current ITI practices in haemophilia A

The NAITR observations, as outlined, have contributed substantially to the current practice of ITI for severe haemophilia patients with inhibitors. The international ITI study, initiated in July 2002, is the only prospective randomized multicentre trial of ITI. The intent of the I-ITI trial is to randomize 150 good-risk paediatric severe haemophilia A patients aged less than 8 years with inhibitors present for less than 4 months to receive either high- (200 U Kg⁻¹ day⁻¹) or low-dose (50 U kg⁻¹ day⁻¹) FVIII. Success is defined by a negative inhibitor titre (<0.6 BU mL⁻¹; <0.3 BU mL⁻¹ by the Nijmegen method) and normal FVIII recovery (≥66% of expected) and half-life (≥6 h) [25]. The trial was designed to prospectively test a hypothesis raised by previously published retrospective meta-analyses of the International and North American ITI registries suggesting that outcome was independent of dosing regimen in good-risk high titre inhibitor patients with severe haemophilia A (historical peak titre ≥5 BU mL⁻¹ and ≤200 BU mL⁻¹; and starting titre of <10 BU mL⁻¹) [20,26]. Currently, 96 centres in 25 countries from North America, Western Europe, Oceania and Asia have recruited 105 subjects in the study (I-ITI study update, World Federation of Haemophilia, Istanbul, 2008).

Furthermore, three independent groups have since developed consensus recommendations for the current practice of ITI in patients with severe haemo-

philia A and high titre inhibitors based on a critical review of the existing literature that included the published findings from the NAITR. These include the European Haemophilia Therapy Standardisation Board (EHTSB) [27]; the International Consensus Panel (ICP) on immune tolerance [28] and the United Kingdom Haemophilia Centre Doctors Organization (UKHCDO) [29].

All have agreed that despite the importance of beginning therapy soon after inhibitor confirmation, deferring the initiation of ITI initiation the titre is <10 BU is preferable. The UKHCDO and the ICP further recommend avoidance of FVIII exposure and the use of non-anamnestic bypass therapy for the prevention and treatment of bleeding during the deferral period [28,29]. However, given the lack of prospective data on the role of pre-ITI titre on outcome, the ICP included in its recommendations the caveat that ITI be started at >10 BU if the titre does not decline over a period of 1–2 years and/or if inhibitor development or persistence is associated with severe or life-threatening bleeding [28].

All groups have also agreed that insufficient information currently exists to make strong recommendations about the initial ITI dosing regimen [27–29]. There was uniform consensus about a critical need for reliable unbiased data, and each group independently recommended that all ITI patients be enrolled either in a prospective randomized clinical trial or an international registry. The ICP further noted that for poor-risk ITI patients defined by a historical titre of >200 BU and/or a pre-ITI titre of >10 BU and/or an interval of >5 years since inhibitor diagnosis, efficacy data is limited to dosing regimens of $\geq 200 \text{ U kg}^{-1} \text{ day}^{-1}$ [16,28]. Participation in prospective comparative clinical trials for such patients was strongly supported by all three groups, as was a trial of dose maximization for patients failing low dose ITI [27–29].

All groups independently concluded that ITI has been successfully performed using recombinant and plasma-derived FVIII replacement therapy (and usually the product on which the patient developed the inhibitor), and that, despite some data to the contrary [30–41], there are no published data to support the superiority of any single product type for ITI or a change in practice [27–29]. The EHTSB and ICP added that concentrates containing von Willebrand factor should be considered for patients who fail ITI using high purity FVIII [27,28].

Furthermore, the EHTSB and ICP have recommended that there is no role for IM in primary ITI [27,28]. Whereas the EHTSB concluded that it could

not recommend rituximab as an alternate ITI strategy without accrual of additional experience with the drug [27], the ICP suggested that rituximab be considered in the case of ITI failure based on anecdotal data [42–45], but in conjunction with participation in an ongoing clinical trial or registry [28].

Finally, although there have been no current recommendations with respect to optimizing the maintenance of tolerance once it is achieved, the I-ITI study has incorporated a 12-month period of ongoing observation on prophylaxis to prospectively ascertain the frequency of relapse following successful tolerance induction [25].

Haemophilia B

Therapeutic regimens. Seventeen ITI courses in severe haemophilia B subjects (81% with high titre antibodies) were reported to the NAITR; 16/17 (94%) courses were completed at the time of analysis. Although 47% of inhibitor development occurred on high purity/monoclonal FIX concentrates, 14/17 (82%) of the ITI reported involved the use of these concentrates. The mean ITI dose of FIX was $100 \text{ U Kg}^{-1} \text{ day}^{-1}$ (range: 25–200). Daily dosing regimens were used in 15/17 (88%) courses. IM was added to 8/17 (47%) of the ITI courses and plasmapheresis was used on two occasions. Subjects who completed therapy were treated for a mean 11.6 months, significantly in less time than those with haemophilia A ($P = 0.05$). This cohort initiated ITI at a mean 44 (1–227) months following inhibitor diagnosis, a slightly shorter interval compared with those with haemophilia A. Haemophilia B subject demographics are included in Table 1 [21].

Outcome data. Of the 16 completed ITI courses, only 5 (31%) were successful using a mean FIX dose of $100 \text{ U kg}^{-1} \text{ day}^{-1}$ (range: 43 to 200) [21]. This included one subject with an inhibitor-associated allergic phenotype. Of these, 4/5 subjects were known to have maintained tolerance on FIX regimens of $25\text{--}100 \text{ U kg}^{-1} \text{ day}^{-1}$ [24].

Outcome predictors. Potentially important outcome parameters are described in Table 4 for the 16 completed ITI courses administered to inhibitor subjects with haemophilia B. Of note, 5/11 subjects who failed ITI had a positive family history of inhibitors compared with none of the successes (Table 4). Importantly, adverse reactions (8/11), including allergic manifestations (4/11) and access complications (9/11) were much more common

Table 4. NAITR: comparison of outcome parameters between haemophilia B subjects who successfully and unsuccessfully underwent immune tolerance induction (ITI).

Haemophilia B ITI outcome	Success (<i>n</i> = 5)	Failure (<i>n</i> = 11)
Factor IX activity <0.01 U mL ⁻¹	5/5	11/11
High responder (<5 BU)	4/5	9/11
Family history of inhibitor	0	5/11
African-American ethnicity	2/5	2/11
Median age (years) at ITI	3.7	4.6
Median interval inhibitor/ITI (months)	12	47
Median ITI factor IX dose (U kg ⁻¹ day ⁻¹)	100	75
Median duration of ITI (months)	12	7
Access complications	0/5	9/11
Adverse reactions	2/5	8/11
Allergic reactions	1/5	4/11

amongst subjects who failed ITI (Table 4). Because of the few evaluable outcomes in this group, only trends could be observed in variables such as pre-induction and historical peak titres and peak titre on ITI, all of which were statistically significant predictors of success in haemophilia A (Table 4) [21].

Adverse events. Fourteen adverse events complicated 11/17 (65%) ITI courses in haemophilia B subjects. This frequency was 10 times higher than that reported with haemophilia A (Table 5). However, as with haemophilia A, there was no statistically significant relationship between ITI factor dose and the adverse event rate (Table 5). Allergic reactions were more common than with haemophilia A ITI and accounted for 11/14 (79%) adverse events and occurred in the 10 registry subjects already known to exhibit allergic reactions to FIX products, subsequent to the development of a FIX inhibitor (Table 5). Of those, 3/11 were severe and the cause of premature cessation of ITI (Table 5). By contrast, adverse events in general and allergic reactions in particular were not responsible for any haemophilia

A ITI failures (Table 5). Furthermore, nephrotic syndrome was not reported in the haemophilia A cohort (Table 5). There were no viral seroconversions [21].

An association between ongoing ITI in FIX inhibitor subjects with a known allergic diathesis and the development of nephrotic syndrome was observed in three individuals. In 1/3 subjects, this complication resulted in immediate cessation of ITI and was the direct cause of failure to tolerate. In all three, symptoms of periorbital oedema, proteinuria and hypoalbuminaemia developed 7 to 9 months into the course of ITI whilst receiving 100 U kg⁻¹ day⁻¹ of either intermediate purity or monoclonal FIX. All exhibited a significant decline in inhibitor titre at the time of diagnosis of nephrosis; all had minimal clinical responses to steroid therapy. One subject's symptoms improved with cessation of ITI [21]. The poor outcome and complications with ITI in allergic phenotype FIX inhibitor patients has since been particularly associated with large or complete deletions in the FIX gene [46,47].

NAITR contributions to current ITI practices in haemophilia B

Based on the poor outcomes highlighted by the NAITR, with corroborating data from The International Society on Thrombosis and Haemostasis (ISTH) Registry on FIX Inhibitors as well as Ewenstein *et al.*, [48–50], the EHTSB, ICP and UKHCDO have all concluded that the success of ITI in eradicating FIX inhibitors is low, particularly in patients with the allergic phenotype, and have recommended that all attempts at ITI in such patients should be cautiously undertaken in conjunction with close clinical monitoring for complications [27–29]. The ICP recommendation specifies the following practice guidelines:

Desensitization may be needed prior to ITI initiation, but this process does not transform risk from poor to good nor does it preclude the development of nephrotic syndrome. The decision to attempt ITI for FIX inhibitors must be very carefully weighed against the relatively high risk of adverse reactions and the relatively low likelihood of success, particularly in those patients whose inhibitor is associated with an allergic phenotype. Consequently, if immune tolerance is initiated, particularly in that subset of patients, physicians are urged to proceed with great caution and to perform routine urinalyses during ITI to detect proteinuria and early nephrotic syndrome [28].

The particularly poor outcome and complications with attempted tolerance induction in patients with

Table 5. NAITR: comparison of adverse events between haemophilia A and B cohorts.

	Haemophilia A	Haemophilia B
Adverse event (AE) rate (% courses)	10/171 (6%)	11/16 (65%)
Allergic reaction (% AEs)	6/14 (4.3%)	11/14 (79%)
Reason for ITI failure (% of all failures)	0/49 (0%)	3/11 (27%)
ITI-related nephrotic syndrome	0/164 (0%)	3/16 (20%)
Adverse event/dose relationship (<i>P</i>)	<i>P</i> = 0.14	<i>P</i> = 0.09

ITI, immune tolerance induction.

FIX inhibitors and an allergic phenotype has recently been reviewed [51–53]. Alternative approaches to this unusual but severe complication of haemophilia B are required. An aggressive immunosuppressive strategy for the treatment of such patients has recently been published [54]. The initiation of a combination of mycophenolate-mofetil, dexamethasone, intravenous immunoglobulin and high dose FIX replacement induced complete tolerance in one patient and resulted in partial success in the second patient. Importantly, FIX replacement therapy was tolerated without any allergic manifestations and neither of the patient developed nephrotic syndrome whilst on ITI.

Conclusion

In summary, the NAITR accomplished its goal in characterizing ITI practices, outcomes, outcome predictors and complications in a large North American population of haemophilia A and B inhibitor patients. However, the retrospective registry was limited in its capacity to provide definitive answers to the many unresolved ITI practice issues. Nonetheless, it played an important role in developing guidelines for the current practice of ITI and, most importantly, in generating hypotheses that must now be rigorously examined through well-conceived and -executed prospective data collection efforts. For haemophilia A, the logical next step has been the international prospective randomized study of outcome relative to FVIII dose for subjects with high titre, but good ITI risk inhibitors. A similarly designed trial on the role of product purity in high-titre poor-risk haemophilia A inhibitor patients will soon begin (A. Gringeri, personal communication). Both trials will additionally provide platforms for translational study of the immunology of tolerance induction, a prelude to the next generation of safe and effective tolerizing strategies.

For the less common problem of inhibitor eradication therapies haemophilia B, prospective randomized studies will not be a feasible way to confirm the NAITR observations. However, coordinated international efforts will still be required to prospectively collect data on ITI outcome to document new potentially effective therapeutic strategies for inhibitor eradication. These registries will hopefully also serve to identify potential subjects for the scientific study of the immunology of haemophilia B-related allergic phenomena. Collaboration between basic and clinical scientists will again be crucial in understanding and effectively treating this devastating complication of FIX antibody development.

Professor Brackmann led the way through astute observation and early documentation of the efficacy of immune tolerance therapy. It is now up to the haemophilia scientific community to continue his groundbreaking work through development and clinical substantiation of the inhibitor eradication and prevention strategies in the future.

Disclosures

The author stated that she had no interests which might be perceived as posing a conflict or bias.

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