The principal results of the International Immune Tolerance Study: a randomized dose comparison

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On behalf of the ITI Study Group

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Running title: International Immune Tolerance Study
Abstract

The International Immune Tolerance (I- ITI) Study was a multicenter, prospective, randomized comparison of high- (HD) (200 IU/kg daily) and low-dose (LD) (50 IU/kg thrice weekly) FVIII regimens in 115 “good-risk” severe high-titer inhibitor hemophilia A subjects. Sixty-six /115 subjects reached defined study end points: success 46 (69.7%); partial response 3(4.5%); failure 17(25.8%). Successes did not differ between treatment arms (24/58 LD vs. 22/57 HD, p=0.909). The times taken to achieve a negative titer (p=0.027), a normal recovery (p=0.002) and to achieve tolerance (p=0.116. NS) were shorter with HD ITI. Peak historical (p = 0.026) and on-ITI (p=0.002) titers correlated inversely with success but only peak titer on ITI predicted outcome in a multivariate analysis (p=0.002). LD subjects bled more often (OR 2.2 p= 0.0019). The early bleed-rate/month was 0.62 (LD) and 0.28 (HD) (p=0.00024), decreasing by 90% once negative titers were achieved. Bleeding was absent in 8/58 LD vs. 21/57 HD subjects (p=0.0085). Central catheter infections (n=124) were reported in 41 subjects (19 LD); infection frequency did not differ between treatment arms. Neither bleeding nor infection influenced outcome. Although stopped early for futility and safety considerations, this trial contributed valuable data toward evidence-based ITI practice.
Introduction

The only proven strategy for achieving antigen-specific tolerance to factor VIII (FVIII) is immune tolerance induction (ITI). Successful ITI leads to normalization of the FVIII pharmacokinetics with consequent improvement in the patient’s quality of life. Our current knowledge about ITI in severe hemophilia A is derived from small cohort studies1-6 and retrospective national and international ITI registries7-9. ITI success rates of 53-79% have been reported10.

ITI outcome is influenced by host and treatment-related variables. The International Immune Tolerance Registry (IITR), the German Registry and the North American Immune Tolerance Registry (NAITR) have all identified parameters of the host immune response to FVIII that influence outcome. Lower pre-ITI (< 10BU), historical peak and, peak titers on ITI, all strongly correlated with ITI success and time to success7-9. Ethnicity and F8 genotype, on the other hand, have not been clearly shown to affect outcome9, 11, 12.

Potential treatment-related ITI outcome variables include bleeding, central venous catheter device (CVAD) infection, FVIII type and dosing regimen. Although CVAD infections have been repeatedly reported to adversely affect ITI outcome13-18, they did not predict ITI outcome in the NAITR9. The impact of bleeding has never been examined.

A retrospective analysis of the Frankfurt experience suggested a better outcome when plasma-derived, VWF-containing, factor VIII was used19. This was not confirmed by either the IITR or the NAITR7, 9, however, and tolerance has been achieved using either recombinant or plasma-derived FVIII20-27. Furthermore, successful ITI with VWF-containing FVIII products may be influenced by antibody epitope specificity28-30.
The role of FVIII dosing regimen in ITI has generated the greatest debate, despite the absence of definitive data. Doses between 50 IU FVIII/kg thrice weekly and 300 IU/kg daily have been used with comparable results\textsuperscript{1-9}. The IITR and NAITR generated conflicting data\textsuperscript{7, 9}. In the IIITR, FVIII doses of \( \geq 200 \) U/kg/day resulted in greater success\textsuperscript{31} whereas the NAITR reported an inverse relationship between FVIII dose and ITI success\textsuperscript{9}. A meta-analysis of both registries determined that, for patients with historical inhibitor titers < 200 BU and immediate pre-ITI titers <10 BU, outcome was uninfluenced by dose\textsuperscript{32}. These parameters have therefore been used to define a ‘good risk’ subgroup of ITI patients. Other predictors of better outcome, including younger age at ITI initiation\textsuperscript{7, 9}, an interval < 5 years between inhibitor diagnosis and ITI start\textsuperscript{7, 9}; and ITI interruption of < 2 weeks duration\textsuperscript{8}, further define a ‘good risk’ subset of patients undergoing ITI.

Although ITI practice guidelines were developed on the basis of low-level published evidence\textsuperscript{33-36}, in the absence of prospective controlled trials, the optimum ITI dosing regimen has never been established. Broader availability of ITI may require a better understanding of the relative efficacy, morbidity and cost effectiveness of current ITI regimens, however.

We present the principal results of a randomized controlled comparison of high- and low-dose immune tolerance induction in a good risk cohort of severe hemophilia A high titer inhibitor subjects. This study was designed to test the hypothesis that overall response to ITI is independent of FVIII dosing regimen in ‘good risk’ subjects. The study also investigated several questions raised in the literature about potential predictors of ITI outcome, and morbidity of ITI.
**Subjects and Methods**

**Subjects:** Subjects with severe hemophilia A (FVIII < 0.01 IU/ml) were recruited from 70 centers in 17 countries between 1/7/02 and 13/11/09, when the study was terminated. The inclusion criteria are summarized in Table 1. Participating centers also submitted basic data on inhibitor subjects not recruited to the ITI study so that we could discover the reasons for non-recruitment and detect recruitment bias.

**Methods:** Subjects were recruited as soon as possible after inhibitor detection and inhibitors checked locally every four weeks. The protocol specified that bleeding should be treated with non-anamnestic bypass therapy prior to ITI. The study plan is summarized in Figure 1. The study was approved by the institutional review boards of all participating hospitals. Written informed consent was obtained in accordance with the Declaration of Helsinki. Patients were computer randomized using the method of minimization, minimizing for product type (recombinant or plasma-derived) and starting inhibitor titer above/below 5 BU/ml. Randomization was deferred until the inhibitor titer had declined below 10 BU/ml. Subjects were randomized to ITI with either 50 IU/kg FVIII thrice weekly (low dose, LD) or 200 IU/kg FVIII daily (high dose, HD). Factor FVIII dose-compliance was monitored and a 20% variance from the total ITI dose was permitted.

The choice of recombinant (rFVIII) or plasma-derived FVIII (pdFVIII) brand used for ITI and the use and management of central venous access devices (CVAD) were at the discretion of the managing clinician. Switching of FVIII brands during the course of ITI was not permitted. Immune tolerance continued for a minimum of 9 and maximum of 33 months. FVIII used in the study was supplied...
through each country’s national or regional health service. FVIII subsidies were negotiated with suppliers for subjects in the United States, Japan and Argentina. In the US, subsidized clotting factor was distributed to participating subjects through Gulf States Pharmacy, University of Texas Medical School at Houston.

After starting ITI, inhibitor measurements were conducted locally once monthly by either the Bethesda or Nijmegen modification assay. Once the inhibitor had been confirmed to be negative, FVIII recovery was measured monthly following an infusion of 50 U/kg of FVIII, without a washout period. Once FVIII recovery was shown to be $\geq 66\%$ of expected, a FVIII half-life study was conducted using 50U/kg of FVIII, following a three-day treatment-free washout period and repeated, if necessary, every twelve weeks until $\geq 6$ hours. Half-life was calculated centrally using Win-Non-Lin software (Pharsight, St Louis, USA) from values obtained pre-infusion; and 15-30 minutes, one, two, four, 6, 24 and 48 hours post-infusion.

The study definitions of successful tolerance, partial response, study failure and relapse are described in Table 2.

Once tolerance was achieved, subjects were changed to prophylaxis, using 30 IU/kg FVIII thrice weekly, and monitored for inhibitor recurrence for a further 12 months. HD subjects tailed down to this dose over three months. Subjects were monitored quarterly using inhibitor titer and FVIII recovery measurements. A FVIII half-life was also requested at the end of the study. Patients were managed and centralized decisions reached on the basis of local inhibitor determinations. Critical inhibitor measurements e.g. starting titer, first negative titer etc. were confirmed centrally by The Hematology Laboratory, Radboud University
Nijmegen Medical Centre, Netherlands, using the Nijmegen modification of the Bethesda assay with a lower limit of detection of 0.2 BU/ml.

**Data Handling and Statistical Analysis:** Data was collected electronically. Clotting factor usage, intercurrent bleeding, surgery, hospitalizations, concomitant medications, all infections, and any other adverse events were documented prospectively. For the purpose of analysis, ITI was divided into four phases These were: **Phase 1:** from the start of ITI until the inhibitor titer was negative; **Phase 2:** from end of phase 1 until the factor VIII recovery was ≥66% of expected; **Phase 3:** from the end of phase 2 until tolerance was achieved; and **Phase 4:** the 12-month period of prophylaxis post-tolerance induction.

Statistics were conducted at the Christie Hospital and Patterson Institute Clinical Trials Unit, using SPSS V 16 and S-Plus 2000. All 2-arm comparisons used the Mann-Whitney U-test. Cumulative bleeds over time were analyzed using the Cox frailty model and survival times were analyzed using the log-rank test. The relationship between variables and the outcome of ITI was analyzed by logistic regression.

The original power calculation, based on the literature, indicated that a sample of 75 subjects per treatment arm would have 80% power at the 0.05 significance level by two-sided log rank test to detect a treatment arm difference, if 80% of the "high-dose" group and 50% of the low-dose group achieved tolerance after 9 months ITI. This calculation assumed the loss of up to 5 subjects per treatment arm and two interim analyses.

Serious adverse events and two interim safety and efficacy analyses were adjudicated prospectively by an independent Data Safety Monitoring Board (DSMB), following a
DSMB Protocol. Interim analyses were conducted when 50 and 100 subjects had reached a primary study endpoint for the evaluation of the DSMB, with investigators remaining blinded.
Results

Subject Accrual and Demographics

A hundred and thirty-four subjects were enrolled at the time of study closure (Figure 2). An additional 171 patients managed by 55 centers not recruited to the study, were reported to us, of whom 161 were ineligible based on one or more subject exclusion criteria. Ten otherwise eligible subjects were not recruited because of clinicians’ concerns about randomization.

Ten of 134 enrolled subjects were lost to the study before randomization. Four of these took longer than the prescribed limit for the inhibitor to decline to < 10 BU/ml. The inhibitor titer rose to >200 BU/ml in one. Consent was withdrawn in four. There was one death from a traumatic intracerebral bleed. Eight further subjects had not been randomized at the time of study termination.

Although 116 subjects were randomized, one was withdrawn by the investigator without starting ITI and therefore excluded from this analysis. Ultimately, 115 subjects started ITI at a median age (IQ range) of 15.5 months (11.0-24.0; 58 LD and 57 HD. Figure 2). Of these, 108 (94%) were randomized sufficiently prior to study termination to have sufficient data for analysis of therapeutic efficacy and safety. Randomized subject demographics did not differ between treatment arms (Table 3).

Among the 115 randomized subjects, the median (IQ range) time for the inhibitors to decline to < 10 BU/ml from the time of first detection was 5.5 months (3.1-8.4).

At the time of study termination, 37/115 (31%) randomized subjects remained on-study, 9 of whom were tolerant but still in the prophylaxis phase of the study. (Figure 2).
Seventy-eight (68%) of 115 randomized subjects had reached an off-study endpoint at the time of study termination (Figure 2). Thirty seven achieved tolerance. Three subjects met the criteria for partial success, and 17 failed ITI (Figure 2).

Twenty-one (18%) randomized subjects were withdrawn for other reasons before reaching a defined study end-point (8 withdrawn by physicians or parents; 12 poor compliance or major protocol violations such as a major dose-change; one lost to follow post-tolerance (Figure 2). Withdrawals were balanced by treatment arm (12 HD and 9 LD withdrawn after a median (IQ range) of 19 (9-27) and 15 (9-17) months, respectively). Twelve subjects were lost to follow-up during the prophylactic phase (8 due to failure to comply or gross protocol deviation (most commonly ceasing regular follow-up); 2 withdrawn by the parent or investigator; and 2 lost to follow-up). Losses post-tolerance were also balanced by treatment arm (6 HD and 6 LD after a median (IQ range) of 16.5 (8.8-30) and 26.5 (24-32) months of treatment, respectively).

RFVIII was used for ITI in 102/115 (90%). Product type was equally distributed between treatment arms (rFVIII in 52 LD and 50 HD; pdFVIII in 7/13 HD and 6 LD subjects).

FVIII dose compliance met study requirement for 89/108 (82%) subjects for whom we had sufficient follow-up for analysis. Four LD subjects exceeded required dose by a median of 32%, and 15 (12 HD) received a median of 49% less FVIII than required by protocol.

Between zero and four confirmatory samples were requested from each subject, depending on how far through the study the patient had progressed. In the end, 139/160 (86.8%) confirmatory samples were retrieved for central testing from 63/115 randomized subjects. These confirmed study decision points, which were
originally based on local testing, with two exceptions. Two subjects had a Bethesda titer of 10.1 and 10.6 BU/ml at the time of randomization.

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**ITI Efficacy: Overall Success and Time to Success**

Sixty-six subjects reached an ITI success, partial success or failure endpoint. Forty-six (69.7%) achieved tolerance, including 9 subjects that were still on study in the prophylaxis phase. Three (4.5%) achieved partial success and 17 (25.8%, 12 HD) failed. A Kaplan-Meier plot of 66 subjects achieving a success, partial success or failure end-point shows no significant difference between treatment arms in the proportion (70%) achieving tolerance or in the time taken to achieve tolerance (figure 3a; p=0.096). A similar proportion achieved tolerance in each arm when all evaluable subjects were included in the analysis, including those lost to the study for logistic reasons, (24/58 (41%) LD; 22/57 (39%) HD, (p=0.909). An intention to treat Kaplan-Meier comparison of time to achieve tolerance including all 115 randomized, treated, subjects shows a lower success-rate, with no significant difference in overall success rate or the time taken to achieve tolerance between treatment arms (Figure 3b; p=0.942).

This sample size had the power to prove equivalence only with a 30% boundary of equivalence (1-tailed, p=0.05). Consequently, equivalent efficacy between high- and low dose ITI could not be statistically established.

Phases 1 and 2 of ITI were significantly longer for the LD than the HD subjects (Table 4, p = 0.027 and 0.002 respectively), although the overall time to
achieve tolerance was not significantly different between treatment-arms (Table 4 p=0.096).

The mean FVIII recovery, post-tolerance, was 91.6%, [median, (IQ-range) 86% (77.3-99.7)] of expected and was near normally distributed (Figure 4a). The mean post-tolerance half-life was 7.8 hours, [median (IQ-range) 7.3 hours (6.73-8.56)]. The distribution of half-life for the group was skewed towards the lower end of the normal range (Figure 4b). There was no difference in the post-tolerance half-life between the low- and HD-arms, which were median (IQ range) 7.39 (6.62-9.03) and 7.21 (6.84-7.77), respectively.

**ITI Efficacy: Partial Success and Relapse**

Three subjects (2 LD) had a partial response to ITI after 33 months of treatment. All responded clinically to FVIII without an increase in inhibitor titer. All had negative inhibitor titers but persistently diminished FVIII recoveries of 52.8%, 36.3% and 49% of expected.

Six subjects partially relapsed, two transiently and four permanently, during the 12-months following tolerance induction (3 HD and 3 LD). Their median (range) recovery and half-life at the time of tolerance was similar to the group as a whole, (median 92.5% (70.2-101.5) recovery; median 7.0 hour (6.0-9.0) half-life).

Relapse occurred at a median 9.5 (2-13) months from the time of tolerance. The inhibitor titer rose transiently to 1.4 BU/ml in one but remained undetectable in the remainder. FVIII recovery was reduced in five cases to 27%, 45%, 45% 52.5%, and 61% of expected and in one recovery was normal (91%) but half-life decreased to 5.3 hours at the time of relapse. Two of 6 had normal pharmacokinetics by the end of the study and are now considered tolerant. The remaining four relapsed subjects
continue to respond clinically to FVIII without anamnesis and therefore fulfill the criteria for partial response.

**Variables Influencing the Outcome of ITI:**

Logistic regression was used to analyze the effect of several variables on overall ITI success and time to successful tolerance (Table 5). The only variables significantly linked with successful ITI in the univariate analysis were the peak historical inhibitor titer and the peak titer on ITI (p = 0.026 and 0.002, respectively). In the multivariate analysis, however, only the peak inhibitor titer on ITI was a significant predictor of ITI outcome (p = 0.002). Time to successful ITI was also analyzed in a Kaplan-Meier comparison of peak historical titer, starting titer and peak inhibitor titer on ITI; age at randomization, presence or absence of infection, Again, only peak historical titer and peak titer on ITI significantly influenced the time taken to achieve tolerance (Figures 5a and 5b, p= 0.006 and 0.001).

**ITI Morbidity: Serious (SAEs) and Non-Serious Adverse Events (AEs)**

In all, 300 SAEs in 71 subjects were reported. Of these, 299 were categorized as SAEs only because they involved hospitalization. Thirty eight (12.7%) were judged by the DSMB to be study-related, and 262 were deemed non-study related. These, and 209 AEs, are summarized in Table 6.

**ITI Morbidity: Central Venous Access Device (CVAD) Infection**

183 catheters were placed in 99 subjects, who had a median of 1; mean 1.6 (range 0-8) catheters. CVADs were placed for routine care before randomization in 73% of subjects. Eighty -two (45%) of the catheters were placed in 47 (81%) LD
subjects, while the remainder were placed in 52/57 (91%) of HD subjects. Eleven LD and 5 HD subjects were managed without a CVAD throughout ITI. Among the 93 subjects for whom catheter type was identified, 72 (77%) were Port-a-Caths.

A total of 124 CVAD infections were reported among 41 subjects; 69 infections occurred among 19 subjects in the LD arm (median 2, mean 3.6 [range 0-11 per subject]), while 22 HD subjects experienced a total of 55 infections (median 1, mean 2.5 [range 0-7 per subject]). In all, 58 (59%) subjects with catheters (28LD; 30 HD) had no CVAD infection while on ITI.

The time from randomization to the first CVAD infection was similar in the two arms. CVAD infections were commoner in patients with external CVADs (Broviac, Hickman and peripheral intravenous lines) than with Port-a-Caths and similar implantable devices (implanted vs. all non-implanted CVADs, p= 0.026).

The effect of central catheter infection on the outcome of ITI was analyzed in 93/99 subjects with a CVAD and adequate data. No difference was found in the proportion of infected subjects with catheters who achieved tolerance (44%; 9/19 LD and 9/22 HD) compared with those never infected (48%; 13/26 LD and 12/26 HD). Furthermore, there was no significant difference in the time taken by infected or non-infected subjects to reach phase 2 of ITI (7.6 v 5.7 months), phase 3 (9.3 v 9.4 months) or phase 4 of ITI (tolerance; 15.3 v 14.9 months).

**ITI Morbidity: Intercurrent Bleeding**

In all, 966 bleeding episodes were recorded for the entire cohort. Although the single death on the trial occurred from a traumatic intracranial hemorrhage prior to the start of ITI, only 65 (7%) of all recorded bleeds resulted in hospitalization, and none were determined by the DSMB to be study-related.
There were significantly more bleeds in the LD than in the HD treatment arm (Table 7) with a hazard ratio for all types of bleeds of 2.20, p = 0.0019. The hazard ratio remained almost unchanged when nine patients using bypass therapy prophylaxis were excluded from this analysis (hazard-ratio 2.01, p = 0.016). Most (84.5%) bleeds occurred during phase 1 of ITI, with significantly more bleeding in the LD arm, (p= 0.0046). Although more hemorrhage was also observed in LD subjects throughout phases 2, 3 and 4 (Table 8), these differences were not significant. This pattern was seen for hemarthroses, muscle bleeds and non- musculoskeletal (other) bleeds when analyzed separately (data not shown).

The difference in the number of bleeds between the treatment arms was largely attributable to a two-fold difference in the bleeding rate per month (table 10). The mean bleed-rate in phase 1 was 0.623 bleeds/month in the LD arm and 0.282/month in the HD arm (p = 0.00024). The bleed rates in phases 2, 3 and 4 of ITI were very much lower and not significantly different between treatment-arms (Table 8). Eight LD subjects and 21 HD subjects had no bleeding during the course of ITI (8/58 v 21/57, p=0.0085). There were 72 hospitalizations for bleeding in the LD arm and 39 in the HD arm (Mann-Whitney U-test, p = 0.145). The DSMB recommended immediate cessation of the study for reasons of safety on the basis of these data.

Bypass-therapy prophylaxis was used at the managing physician’s discretion. Seven LD subjects and two HD subjects were treated with bypass-therapy prophylaxis in standard dosage for between three weeks and 19 months during phase 1 of ITI. We currently have insufficient data to evaluate the relative efficacy of prophylaxis in this group.

The comparative pharmacoeconomic analysis of the two treatment arms is ongoing and will be reported separately.
Discussion

We report the results of the first prospective, randomized trial of ITI in patients with severe hemophilia A and high titer inhibitors. We hypothesized that HD ITI would achieve tolerance more rapidly than LD ITI but would have a similar overall success-rate. As expected, the success rate was statistically similar between treatment arms. The study lacked the statistical power required by a comparative trial to demonstrate therapeutic equivalence below the 30% boundary of equivalence.

The tolerance rate reported for this study is lower than reported for many other series. This is the first ITT analysis of immune tolerance, however, and includes subjects unable or unwilling to complete ITI, reflecting the previously unreported treatment adherence difficulties encountered in normal clinical practice. Furthermore, due to the fixed and well-defined study end-points required of a comparative trial, subjects who did not achieve the determinants of success after 33 months on ITI or whose titers declined more slowly than allowable on study were reported as failures, although some may have subsequently achieved tolerance through continued treatment off-study. Furthermore, the 12% of subjects determined in this trial to be partial responders would have classified as “successes” by the less stringent endpoints used in previous studies. For instance, although the NAITR reported an 83% success rate among ‘good risk’ subjects, 87% of registry participants were so defined solely on the basis of a negative inhibitor titer. For these reasons, the success rate reported in this trial is not directly comparable with earlier uncontrolled retrospective studies.

The time to tolerance for the entire study cohort was similar to that previously reported. HD subjects achieved a negative titer and normal recovery significantly more rapidly than LD subjects, however, and LD subjects required 50% longer to
achieve tolerance overall (NS). The clinical implications of these findings are unclear at this time. Although prolonged ITI could conceivably adversely affect adherence to therapy, treatment compliance and drop-out rate did not differ between treatment arms.

Tolerance was defined as the restoration of normal FVIII pharmacokinetics using a consensus definition. A subsequent report showed that the median half-life and recovery in 52 subjects with a median age of 3.1 +/- 1.5 years, was 9.88 +/- 1.89 hours and 1.90 +/- 0.43 IU/dL. These data were normally distributed, but reflected considerable interpersonal variation. Between the ages of 1 and 6 years, half-life increased by 0.4 hrs per year\textsuperscript{37}. At the time of tolerance, our subjects (mean age of 15.4 months) had a mean FVIII recovery of 90.9\% of expected (range 66-182.9), normally distributed, and mean half-life of 8.0 (IQ range 6.73-8.56), (figures 4a and 4b). Although comparable with patients of similar age lacking inhibitors\textsuperscript{37}, the half-life estimations of ‘tolerant’ subjects in our trial were skewed towards the protocol-prescribed lower limit, either reflecting the comparatively younger age of our cohort, or suggesting that some subjects may have persistent very low-level inhibitor activity that did not compromise response to FVIII replacement.

We also report the first prospectively collected data on the loss of previously normalized pharmacokinetics during the first year after successful tolerance, defined in this study as relapse. Four of 37 (11\%) tolerized subjects exhibited a non-recovered loss of normalized pharmacokinetics at variable times during the prophylaxis phase of study, becoming partial responders. Pharmacokinetics in this group were indistinguishable from the group as a whole when they were originally considered tolerant. Although the NAITR reported a 12\% relapse rate as part of its retrospective
analysis, those patients had completely lost FVIII responsiveness and so are not comparable.38

One of the objectives of the I-ITI study was to investigate potential host- and treatment-related predictors of ITI success in ‘good risk’ subjects using a logistical regression analysis of the effect of these variables on outcome (Table 7). This confirmed historical peak inhibitor titer and peak titer on ITI to be significantly inversely associated with ITI outcome in a univariate analysis. In a multivariate analysis, however, only peak titer on ITI remained a significant determinant of ITI success. These data are consistent with previous reports that a lower historical peak titer7, 9, particularly a lower peak titer on ITI, are significant predictors of successful ITI outcome.9

The study design and subject demographics prevented us from confirming the previously reported relationship between low starting inhibitor titer and successful ITI outcome since our subjects all had a starting titer <10 BU/ml at the time of randomization. (Table 7). A pre-ITI titer of < 10 BU primarily defined the ‘good risk’ ITI subject in both the IITR and NAITR and was therefore an important inclusion criterion for this trial7, 9. This remained a controversial enrolment requirement throughout the trial, however, due to concern amongst some investigators about the potential of inhibitor-related morbidity during the waiting period for inhibitor titer decline. We found that it took a median of only 5 months for the inhibitor to decline to <10 BU/ml and under 9 months for most subjects with historical titers < 200 BU. However, a similar outcome was observed in subjects with a starting titer above and below the median of 6 BU, suggesting that deferring ITI until very low starting inhibitor titers are achieved results in no further improvement in ITI outcome. This
contrasts with NAITR data which suggested that extremely low starting titers were associated with a uniformly good outcome \(^9\).

ITI initiation at an early age was an important determinant of ITI success in the IITR \(^7\), but not in the much younger cohort reported in the NAITR \(^9\). Most subjects in this study were \(<2\) years old, with a restricted age-range. No significant advantage of initiation of ITI at an early age could be demonstrated for this reason.

An important aim of this trial was to establish the morbidity of ITI and to compare the morbidity associated with HD and LD ITI, since there is very little published data on this subject. Over 50\% of serious adverse events (SAEs) reported in this study were CVAD-related events and only 13\% were determined by the DSMB to be study-related. The high prevalence of CVAD-related adverse events during ITI has already been reported in retrospective analyses\(^{15,17}\) and an adverse effect of CVAD infection on the outcome of ITI has also been suggested.

In the I-ITI study, although 86\% of all subjects received ITI through at least one CVAD, 73\% had a catheter placed for routine treatment of bleeding prior to the initiation of ITI. Catheter use did not differ significantly between treatment arms. Unexpectedly, we also observed no differences in the rates of CVAD infection between treatment arms. Although ITI was administered by peripheral venepuncture in twice as many LD subjects (11) as HD subjects (5), this difference was not significant. Moreover, 45\% of all catheters were placed in subjects receiving LD ITI. Implantable devices were significantly less likely to become infected than external catheters, as previously reported \(^{15}\).

Contrary to expectation, we observed no significant impact of CVAD infection on either overall ITI success or the time taken to achieve ITI milestones. CVAD infection has long been anecdotally associated with a non-specific but sometimes
dramatic increase in inhibitor titer and sometimes subsequent failure of previously promising ITI induction. Although not observed in this good-risk cohort, the potential adverse effect of catheter infection on ITI outcome will be further evaluated in poor-risk ITI subjects as part of the ongoing RESIST study 39.

Although ITI induction has anecdotally been observed to offer some protection from intercurrent bleeding, this has never been systematically investigated in a large cohort. The prospective nature of this trial allowed us to collect reliable data to explore the effect of FVIII dose on bleeding frequency. In all, 966 hemorrhagic episodes were reported during this trial. A single non study-related hemorrhagic death occurred prior to the start of ITI. Only 7% of all recorded bleeds resulted in hospitalization, however, none considered by the DSMB to be study-related.

We were surprised to discover a significantly greater number of bleeds with LD compared to HD ITI. Furthermore, significantly more LD subjects required hospitalization for bleeding and significantly fewer experienced a bleed-free course on ITI compared with their HD counterparts. The increased number of bleeds was caused by an increase in bleeding rate and not to the greater duration of phase 1 LD ITI, or to disproportionate use of bypass therapy prophylaxis during HD ITI. The difference in bleed-rate between arms was most marked during phase 1 of ITI, when 85% of bleeding occurred and when the FVIII half-life was presumably shortest. During phase 2 and 3, the bleeding rate declined dramatically in both arms. This pattern was seen for haemarthrosis, muscle bleeds and soft tissue bleeding. These data imply that both HD and LD regimens provide some degree of protection from intercurrent bleeding when the inhibitor has fallen to a low level. More bleeding was observed in LD than HD subjects throughout the study, persisting through prophylaxis.
Detailed pharmacoeconomic analysis and modeling of the results of the I-ITI study may influence the choice of optimal regimen. However, one of the major goals of inhibitor eradication is to minimize lifelong bleeding-related morbidity. Consequently, although global access to ITI is assumed to require the availability of less aggressive FVIII infusion strategies, the future clinical practice of ITI must prioritize early and effective control of bleeding. The prospective study of strategies to minimize bleeding during ITI (e.g. the ENJOIH study) may be a critical next step in optimizing ITI.

The DSMB recommended study termination because they identified bleeding as a safety issue. They also recommended no further recruitment because the power calculation showed that proof of therapeutic equivalence between the two FVIII doses being compared, using a 20%, 15% or 10% boundary of equivalence, would have required 75, 132 or 297 subjects completing each treatment arm. This was not feasible, despite recruitment from 90 centers in 17 countries.

Barriers associated with the conduct of clinical trials in rare disease populations, particularly those relevant to study logistics and subject recruitment, represented major challenges during this trial. Alternative models for clinical trial design may indeed be useful for the design of future interventional trials. Nonetheless, this study has created a precedent and a model which has encouraged other investigators to initiate multinational investigator-led trials in hemophilia, a trend which we hope will continue.
Contributions

CRM Hay and DM DiMichele were co-principal investigators of this study, jointly responsible for study design and oversight, as well as the analysis of data and preparation of this manuscript.

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Conflict of Interest Statement:

CRMH has received unrestricted research/educational funding from Bayer, Baxter, Pfizer and CSL-Behring. DMD has no conflicts of interest.
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Table 1: Study subject inclusion criteria:

1. Severe hemophilia A (VIII <0.01 IU/ml).
2. Peak historical inhibitor $\geq$ 5 BU/ml and $\leq$ 200 BU/ml.
3. Starting titer $\leq$ 10 BU/ml before randomization.
4. Titer declines to $<$ 10 BU in $<$ 12 months ($<$ 24 months from 2006).
5. Age $<$ 8 years at time of randomization.
6. Local and/or central review board approval.
7. Written informed consent.
8. Ability and willingness of subject to comply with the protocol.
Table 2: Study definitions of successful tolerance, partial response study failure and relapse*:

**Successful Tolerance:** Negative inhibitor titer, factor VIII recovery $\geq 66\%$ of expected and factor VIII recovery $\geq 6$ hours.

**Partial Response:** After 33 months of ITI, negative inhibitor titer but persistently abnormal recovery or half-life; responding clinically to factor VIII replacement without an anamnestic increase in inhibitor titre.

**Study Failure:** Failure of the inhibitor to decline by $\geq 20\%$ over any 6 month period after the first 3 months of immune tolerance induction (ITI); or Failure to achieve tolerance or partial response after 33 months on ITI; or Withdrawal from the study for any reason before tolerance was achieved.

**Relapse:** Inhibitor recurrence during the 12 month follow up period on prophylaxis after tolerance was achieved, as evidenced by recurrent positive Bethesda titer or a decline in factor VIII recovery or half life below study limits.

* Consensus Proceedings from the second International Conference on Immune Tolerance Therapy, Bonn 1997, unpublished*
Table 3: Subject demographics for 115 randomized subjects by treatment arm reported as median (IQ Range) except as stated

<table>
<thead>
<tr>
<th></th>
<th>Low Dose</th>
<th>High Dose</th>
<th>p value</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>(n=58)</td>
<td>(n=57)</td>
<td></td>
</tr>
<tr>
<td>Randomization age (months)</td>
<td>15.6</td>
<td>14.4</td>
<td>0.75</td>
</tr>
<tr>
<td></td>
<td>(10.7-23.2)</td>
<td>(11.4-25.3)</td>
<td></td>
</tr>
<tr>
<td>Diagnostic inhibitor titer (BU/ml)</td>
<td>9.9</td>
<td>11.5</td>
<td>0.52</td>
</tr>
<tr>
<td></td>
<td>(5.0-18.2)</td>
<td>(6.3-23.0)</td>
<td></td>
</tr>
<tr>
<td>Peak historical inhibitor titer (BU/ml)</td>
<td>21.7</td>
<td>22.4</td>
<td>0.78</td>
</tr>
<tr>
<td></td>
<td>(13.4-52.5)</td>
<td>(12.5-50.0)</td>
<td></td>
</tr>
<tr>
<td>Inhibitor titer at randomization (BU/ml)</td>
<td>5.9</td>
<td>5.1</td>
<td>0.85</td>
</tr>
<tr>
<td></td>
<td>(3.3-7.3)</td>
<td>(3.0-7.4)</td>
<td></td>
</tr>
<tr>
<td>Peak inhibitor titer on ITI (BU/ml) #</td>
<td>40.1</td>
<td>33.0</td>
<td>0.37</td>
</tr>
<tr>
<td></td>
<td>(7.6-150)</td>
<td>(1.5-205)</td>
<td></td>
</tr>
<tr>
<td>Total time on ITI (months) #</td>
<td>16.4</td>
<td>14.2</td>
<td>0.70</td>
</tr>
<tr>
<td></td>
<td>(10.5-22.4)</td>
<td>(9.1-22.6)</td>
<td></td>
</tr>
</tbody>
</table>

Ethnicity*

<table>
<thead>
<tr>
<th>Ethnicity</th>
<th>Low Dose</th>
<th>High Dose</th>
</tr>
</thead>
<tbody>
<tr>
<td>Caucasian</td>
<td>32</td>
<td>27</td>
</tr>
<tr>
<td>African</td>
<td>5</td>
<td>4</td>
</tr>
<tr>
<td>Asian</td>
<td>12</td>
<td>11</td>
</tr>
<tr>
<td>Other</td>
<td>9</td>
<td>14</td>
</tr>
</tbody>
</table>

BU: Bethesda Units

#: data for 108 subjects

*: ethnicity data missing for one subject
Table 4: Time to achieve ITI milestones by treatment arm reported as median (IQ range) months

<table>
<thead>
<tr>
<th>Phase</th>
<th>N</th>
<th>Low Dose</th>
<th>N</th>
<th>High Dose</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>Phase 1</td>
<td>29</td>
<td>9.2</td>
<td>31</td>
<td>4.6</td>
<td>0.017</td>
</tr>
<tr>
<td><em>(Start of ITI to negative titer)</em></td>
<td>(4.9-17.0)</td>
<td>(2.8-13.8)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Phase 2</td>
<td>27</td>
<td>13.6</td>
<td>23</td>
<td>6.9</td>
<td>0.001</td>
</tr>
<tr>
<td><em>(Negative titer to 1st normal recovery)</em></td>
<td>(8.7-19.0)</td>
<td>(3.5-12.0)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Phase 3</td>
<td>24</td>
<td>15.5</td>
<td>22</td>
<td>10.6</td>
<td>0.096</td>
</tr>
<tr>
<td><em>(Normal recovery to tolerance)</em></td>
<td>(10.8-22.0)</td>
<td>(6.3-20.5)</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
Table 5: Logistic regression: The relationship between subject and treatment variables and the outcome of ITI.

### Univariate Analysis

<table>
<thead>
<tr>
<th>Subject Variables</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ethnicity (Caucasian / non Caucasian)</td>
<td>0.71</td>
</tr>
<tr>
<td>Age at randomization (ITI)</td>
<td>0.83</td>
</tr>
<tr>
<td>Peak historical inhibitor titer</td>
<td>0.026</td>
</tr>
<tr>
<td>Peak titer on ITI</td>
<td>0.002</td>
</tr>
<tr>
<td>Peak Titre on ITI ≤ 250 v &gt; 250 BU</td>
<td>0.0002</td>
</tr>
<tr>
<td>Time to titer of &lt;10 BU, pre-ITI</td>
<td>0.40</td>
</tr>
<tr>
<td>Starting inhibitor titer</td>
<td>0.98</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Treatment Variables</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>Randomized treatment arm</td>
<td>0.82</td>
</tr>
<tr>
<td>Protocol dose compliance</td>
<td>0.35</td>
</tr>
<tr>
<td>Product type</td>
<td>0.58</td>
</tr>
<tr>
<td>Total Hospital in-patient days</td>
<td>0.088</td>
</tr>
<tr>
<td>CVAD in place</td>
<td>0.58</td>
</tr>
<tr>
<td>CVAD infection</td>
<td>0.83</td>
</tr>
</tbody>
</table>

### Multivariate analysis

| Peak inhibitor titer on ITI              | 0.002|
Table 6: Serious adverse events (SAEs) and adverse events (AEs)

38 (12.7%) Study-related SAEs:

- 36 catheter-related events:
  - 15 infections in 7 subjects.
  - 13 insertions/removals
  - 5 malfunctioning catheters
  - 2 catheter site wound dehiscences
- 1 factor VIII reaction.
- 1 trauma

_______________________________________________________________

262 (87.3%) non-study-related SAEs:

- 11 traumas*
- 69 spontaneous bleeds
- 140 catheter-related problems:
  - 75 catheter infections in 23 subjects
  - 43 catheter insertion/removals.
  - 1 subclavian thrombosis.
  - 3 haematomas at injection-site
  - 21 other catheter-related problems.
- 10 infections unrelated to catheters
- 12 fever of unknown origin
- 9 surgeries (inc. 2 dental extractions)
- 2 bronchospasm
- 1 possible factor VIII reaction.
- 5 unspecified

*Including one death from traumatic intracranial hemorrhage, pre-randomization.

_______________________________________________________________

209 AEs:

- 64 catheter-related AEs.
- 80 minor infections.
- 29 fevers.
- 30 traumas.
- 6 unspecified
Table 7: All intercurrent bleeding by treatment arm and phase of ITI

<table>
<thead>
<tr>
<th>Regimen</th>
<th>Bleed#</th>
<th>HR</th>
<th>(95% CI)</th>
<th>p value</th>
</tr>
</thead>
<tbody>
<tr>
<td>All ITI</td>
<td>low dose</td>
<td>684</td>
<td>2.2</td>
<td>(1.34-3.62)</td>
</tr>
<tr>
<td>(n= 58 vs. 57)</td>
<td>high dose</td>
<td>282</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Phase 1</td>
<td>low dose</td>
<td>573</td>
<td>2.27</td>
<td>(1.29-4.01)</td>
</tr>
<tr>
<td>(n= 58 vs. 57)</td>
<td>high dose</td>
<td>241</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Phase 2</td>
<td>low dose</td>
<td>47</td>
<td>3.4</td>
<td>(0.84-13.8)</td>
</tr>
<tr>
<td>(n = 27 vs. 23)</td>
<td>high dose</td>
<td>4</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Phase 3</td>
<td>low dose</td>
<td>9</td>
<td>5.18</td>
<td>(0.71-38.0)</td>
</tr>
<tr>
<td>(n = 24 vs. 22)</td>
<td>high dose</td>
<td>3</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Phase 4</td>
<td>low dose</td>
<td>54</td>
<td>1.70</td>
<td>(0.80-3.63)</td>
</tr>
<tr>
<td>(n = 24 vs. 22)</td>
<td>high dose</td>
<td>32</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Phase 1: from the start of ITI until the Bethesda titer is negative. Phase 2: from phase 1 until the FVIII recovery is normal. Phase 3: from phase 2 to normal half-life. Phase 4: 12-month prophylactic phase after the half-life has normalized.
Table 8: Intercurrent all bleed-rate (bleeds per month) by treatment arm and phase of ITI

<table>
<thead>
<tr>
<th>Phase 1</th>
<th>Dose (n)</th>
<th>Mean</th>
<th>Median</th>
<th>(IQ-Range)</th>
<th>p value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Low (58)</td>
<td>0.623</td>
<td>0.564</td>
<td></td>
<td>(0.093-0.886)</td>
<td>0.00024</td>
</tr>
<tr>
<td>High (57)</td>
<td>0.282</td>
<td>0.000</td>
<td></td>
<td>(0.000-0.440)</td>
<td></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Phase 2</th>
<th>Low (27)</th>
<th>0.127</th>
<th>0.000</th>
<th>(0.000-0.073)</th>
<th>0.283</th>
</tr>
</thead>
<tbody>
<tr>
<td>High (22)</td>
<td>0.087</td>
<td>0.000</td>
<td></td>
<td>(0.000-0.000)</td>
<td></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Phase 3</th>
<th>Low (24)</th>
<th>0.150</th>
<th>0.000</th>
<th>(0.000-0.148)</th>
<th>0.552</th>
</tr>
</thead>
<tbody>
<tr>
<td>High (22)</td>
<td>0.033</td>
<td>0.000</td>
<td></td>
<td>(0.000-0.000)</td>
<td></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Phase 4</th>
<th>Low (24)</th>
<th>0.175</th>
<th>0.150</th>
<th>(0.000-0.290)</th>
<th>0.112</th>
</tr>
</thead>
<tbody>
<tr>
<td>High (22)</td>
<td>0.102</td>
<td>0.000</td>
<td></td>
<td>(0.000-0.231)</td>
<td></td>
</tr>
</tbody>
</table>
Legend to Figures

Figure 1: Flow-diagram summarizing the protocol for the study, randomization, and monitoring of ITI and prophylaxis.

Figure 2: Flow diagram showing the disposition of all 115 patients randomized and started on ITI.

Figure 3a: Kaplan-Meier plot showing the time to tolerance for the 66 patients who achieved a success, partial success or failure end-point, broken down by HD and LD treatment-arm. Each notch represents a patient reaching a tolerance or failure end-point.

Figure 3b: An intention-to treat Kaplan-Meier plot showing the time to tolerance for all 115 patients randomized, broken down by treatment arm. This shows no significant difference between treatment arms (p=0.942), but a lower success-rate since those not completing ITI or withdrawn for logistic reasons are also included.

Figure 4a: Histogram showing the distribution of factor VIII recovery in 46 patients who achieved tolerance, estimated at the point at which the subjects were considered tolerant.

Figure 4b: Histogram showing the distribution of half-life in 46 patients who achieved tolerance, estimated at the point at which the subjects were first found to have a half-life in excess of 6 hours.

Figure 5a: Kaplan-Meier plot showing the time to tolerance of all 115 randomized, treated, subjects categorized according to peak historical titer above and below the median 22 BU/ml. value (p=0.006).

Figure 5b: Kaplan-Meier plot showing the time to tolerance of all 115 randomized, treated, subjects categorized according to peak inhibitor titer on ITI above and below the median 36 BU/ml. value (p=0.001).
Diagnosis (Inhibitor $\geq 5$ and $\leq 200$ BU/ml) Wait till inhibitor $< 10$ BU/ml

Randomize

High

Regimen

Low

200 IU/KG/day

50 IU/KG 3 x week

negative inhibitor. Recovery $< 66\%$. Continue ITI. Recheck recovery monthly

negative inhibitor. Recovery $\geq 66\%$, Check half-life 3 monthly till $\geq 6$hrs.

12 months follow up. Tail off high-dose arm. Inhibitor 3 monthly. Half-life at 12 months.

End of Study

Fig 1.
Fig. 2.

115 Randomized

78 off-study

37 tolerant

3 partial successes

17 failures

21 removed for other reasons

19 Tolerant at end of study

6 relapses (also partial successes)

12 <20% decline in inhibitor in 6 mths.

5 failure to eradicate inhibitor in 33 mths.

12 removed Post tolerance

37 on-study

16 with inhibitor

9 negative inhibitor

3 normal recovery

9 Tolerant on prophylaxis

16 with inhibitor

9 negative inhibitor

3 normal recovery

9 Tolerant on prophylaxis
Fig 3a:

Low-dose
High-dose

P = 0.942
Fig 3b

Time (years)

% Tolerant

Low
High

P=0.942
Fig. 4a

Factor VIII Recovery. % of expected.
Fig. 4b
Fig 5a:

- < 22 BU/ml
- ≥ 22 BU/ml

P = 0.006
Figure 5b:

- < 36 BU/ml
- ≥ 36 BU/ml

P = 0.001
The principal results of the International Immune Tolerance Study: a randomized dose comparison

Charles RM Hay and Donna M DiMichele