Poster W-086

Final Results of the Prospective ADVATE Immune Tolerance Induction Registry (PAIR) Experience with rAHF-PFM

Shapiro AD,[1] Khair K,[2] Teitel J,[3] Doralt J,[4] Goldstine J,[5] Fidell L[6], Gringeri A,[4] Spotts GD[5]

[1]Indiana Hemophilia and Thrombosis Center, Indianapolis, IN, USA; [2]Great Ormond Street Hospital, Haemophilia Centre, London, UK; [3]St. Michael's Hospital, Hemophilia Program, Canada U of Toronto, Toronto, ON; [4*]Shire, Vienna, Austria ; [5*]Shire, Chicago, IL; [6*]Shire, Cambridge, MA

INTRODUCTION

- 20–35% of severe and 3–13% of mild-moderate hemophilia A (hem A) patients develop inhibitory antibodies.[1-9]
- Without intervention, inhibitors can cause unresponsiveness to FVIII therapy and lead to poorer outcomes.[10,11]
- Immune tolerance induction (ITI) regimens of 25–200 IU/kg FVIII daily or alternate days was successful in 70% of hemophilia patients with inhibitors to FVIII.[3-10]
- In inhibitor patients with severe hemophilia, success rates were similar between low-dose (50 IU/kg FVIII, three times a week) and high-dose (200 IU/kg FVIII, daily) regimens. However, patients receiving low-dose ITI took longer to achieve tolerance and had higher bleed rates compared with the high-dose group.[13]
- ADVATE ITI global registry (PAIR) was designed to characterize rAHF-PFM safety and effectiveness for use in ITI in clinical practice; recruitment began in July 2007.

OBJECTIVE

- To assess the safety/tolerability and success of rAHF-PFM during ITI therapy in clinical practice.

METHODS

Study Design

- Prospective, uncontrolled, open-label, non-interventional study
- rAHF-PFM ITI dosing regimen and monitoring schedule at the discretion of the treating physician
- Data collected from patient diaries and clinic visits
- Maximum observation period for ITI is 33 months plus 12-month follow-up outcome assessments after ITI termination

Endpoints

- Primary: Safety of rAHF-PFM during ITI therapy
- Secondary:
  - Success rate of rAHF-PFM ITI[12]
  - Incidence of central venous access device (CVAD)–related infections during rAHF-PFM ITI
  - Correlation of ITI success with subject characteristics, treatment variables, and intercurrent infections

Inclusion/Exclusion Criteria

- Diagnosis of hem A
- Development of an inhibitor to FVIII following the use of any FVIII concentrate
- Physician prescribed rAHF-PFM ITI, independent of decision to participate in PAIR
- No previous failure of ITI therapy and no history of hypersensitivity reactions to FVIII

Safety/Tolerability

- All adverse events (AEs) during rAHF-PFM ITI therapy
- If inhibitor development occurred before rAHF-PFM ITI initiation and had not been reported, the event was reported as a serious AE (SAE)

RESULTS

- As of October 2015, all subjects have exited the study and completed 12-month follow-up. The data presented represents the final data.
- Forty-four subjects were enrolled from 10 countries, 36/44 subjects (81.8%) completed ITI therapy, 31 of these subjects also completed a 12 month follow-up. Thirty-eight of 44 (86.4%) subjects had severe hemophilia A (FVIII ≤ 1%).
- At initiation of ITI, high titer inhibitors (≥ 5 Bethesda Units [BU]) were present in 15 subjects with any hemophilia severity.
- High-titer inhibitors ≥ 5BU, > 10 BU, and > 100 BU, were detected in 35, 28, an 19 subjects respectively before or during ITI.
- Most frequent dose for iITI (in 26 (59.1%) subjects) was 90–130 IU/kg/day (Table 2) and a mean of 5.98 doses per week.
- In subjects who completed ITI treatment, 21 (58.3%) achieved a negative Bethesda titer; two subjects (5.6%) converted from high to low titer inhibitor, and 8 (22.2%) experienced a failure (Table 3).
- Subjects who failed ITI appeared to have higher peak inhibitor titers than those who achieved success.

RESULTS (continued)

- Kaplan-Meier estimated cumulative success rates over 18 months are shown in Figure 1; 72.4% (95% CI 55.5%–87.0%) of subjects were successful per protocol; 68.3% (95% CI 51.8%–83.6%) of completers were successful.
- Median times to first and second negative titers for all subjects were 4.34 months and 5.78 months, respectively; for those with high titer inhibitor median time to first and second negative titer test was 4.78 and 6.74 months respectively.
- A total of 339 bleeding episodes occurred in 33/36 subjects during ITI.
- There were no product related SAEs reported, and no unusual, related non-serious AEs (table 4); non-product related CVAD device complications were common with 18 episodes on local site infection in 5 (11%) subjects and 8 episodes of systemic infection in 5 (11%) subjects.

Table 1: Baseline Demographics

Parameter		Subjects With FVIII ≤ 1% (n = 38)	All Subjects (N = 44 TOTAL)
Median age at ITI start, months (min, max)		19.0 (1.0, 320)	23.5 (1, 676)
Race, n (%)	White	24 (63.2)	29 (65.9)
	Asian	1 (2.6)	1 (2.3)
	Black	4 (10.5)	4 (9.1)
	Hispanic	3 (7.9)	3 (6.8)
	Other/missing	6 (15.8)	7 (15.9)
Family history of inhibitor, n (%)	Yes	10 (26.3)	11 (25.0)
	No	25 (65.8)	30 (68.2)
	Unknown	3 (7.9)	3 (6.8)
Median titer, BU (min, max)	At diagnosis	4.9 (0.7, 173.0)	4.9 (0.5, 173.0)
	Peak before ITI*	12.5 (0.7, 225.2)	12.5 (0.7, 225.2)
	Immediately before ITI	4 (0, 60.6)	3.95 (0, 60.6)

*If peak titer before ITI therapy was not reported, the maximum of all titer measurements made before ITI were used.

Table 2: ITI Dose Regimens

Dose, IU/kg/d	Subjects With FVIII ≤ 1% (Severe Hemophilia A) (n = 38)		All Subjects (N = 44)	
	High Titer, n (%) (n = 26)	Low Titer, n (%) (n = 12)	High Titer, n (%) (n = 29)	Low Titer, n (%) (n = 15)
≥ 200	4 (15.4)	0 (0.0)	4 (13.8)	0 (0.0)
~131–199	2 (7.7)	0 (0.0)	3 (10.3)	0 (0.0)
90–130	16 (61.5)	6 (50.0)	18 (62.1)	8 (53.3)
< 90	4 (15.4)	6 (50.0)	4 (13.8)	7 (46.7)

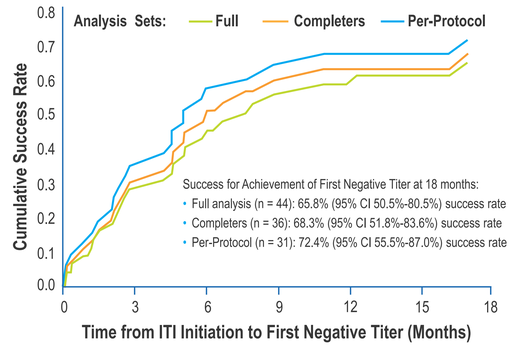
High titer inhibitor: ≥ 5 BU; low titer inhibitor: < 5 BU.

Table 3. Summary of Subject Outcome for ITI Therapy: Completers Analysis

Completers	Severe Hemophilia (≤ 1%) (n = 31)	Non-severe Hemophilia (> 1%) (n = 5)	Total (n = 36)
General success, n (%)	18/31 (58.1)	3/5 (60.0)	21/36 (58.3)
High Titer to Low Titer Conversion, n (%)	2 (6.5)	0 (0.0)	2 (5.6)
Precise criteria, n (%)			
Complete success	NA insufficient PK data*		
Partial success	NA insufficient PK data*		
Failure	7/31 (22.6)	1 (20.0)	8/36 (22.2)

*Few subjects provided FVIII IVR and/or half-life data and thus the sample size was too small for meaningful analysis.

Figure 1: Kaplan-Meier Estimated Cumulative Success Rates Over 18 months



Full Analysis Set
- The full analysis set was comprised of all subjects who enrolled in the study and started ITI therapy.

Completers Analysis Set
- The completers analysis set was comprised of subjects who completed ITI therapy, regardless of completion status of the 12-month follow-up period.

Per-Protocol Analysis Set
- The per-protocol analysis set was comprised of a subset of subjects in the completers analysis set who completed ITI therapy with an assessable outcome as defined in the protocol (e.g. all necessary inhibitor titer results are available in order to determine ITI success/failure).

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SAFETY / TOLERABILITY

- No treatment emergent serious adverse events considered related to rAHF-PFM occurred as per clinical study database snapshot (Table 4).

CVAD Complications

- The most common AEs unrelated to study product reported were associated with CVAD use.
- Thirty-two subjects experienced one or more CVAD-related AE/complications
- CVAD-associated complications occurring in > 1 subject were line insertions, line removal, line insertion site bleeds, infections, and malfunction.

Table 4: AEs Reported During rAHF-PFM ITI

Adverse Events, n (%)	All Subjects (N = 44)
Total AEs	284
Total SAEs	56 (19.7)
Related SAEs	0
Total non-serious AEs	228 (80.3)
Unrelated non-serious AEs	214(75.4)
Related non-serious AEs*	14 (4.9)
Discontinuations, n	
Subject withdrew	2 (4.5)
Physician decisions	1 (2.3)
Lost to follow-up	4 (9.1)
Other	2 (4.5)

*Related non-serious AEs included: pyrexia, urticaria, nausea (n = 2), catheter site pain, upper respiratory tract infection, arthralgia (n = 2), heamathrosis (n = 2) and FVIII inhibition (n = 4).

CONCLUSION

- All subjects have exited the study and completed 12-month follow-up. The final results add knowledge on prognosticators of ITI success.
- rAHF-PFM was effective in a variety of ITI dosing regimens currently used in clinical practice. The most common dose regimen, regardless of hemophilia severity and inhibitor titer, was 90–130 IU/kg/day.
- No product-related SAEs were reported; only 14 related non-serious AEs were seen, none of which would imply any specific safety concern with using rAHF-PFM for ITI.
- Complications associated with CVAD use were commonly reported; education on best practices may be helpful to avoid safety concerns.
- Projected per protocol cumulative success rate at 18 months of 72.4% is consistent with published results in hemophilia A subjects with high-titer inhibitors from the International ITI Study (69.7%).[13]
- These data, along with prior study results,[14] suggest that ITI treatment with rAHF-PFM is both safe and effective.

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