A Post-Authorisation Safety Surveillance of ADVATE, Recombinant Antihemophilic Factor, Plasma/Albumin-Free Method (rAHF-PFM) in Hemophilia A

Yeu-Chin Chen, Shin-Nan Cheng
Tri-Service General Hospital, Taipei, Taiwan

INTRODUCTION

ADVATE, an antihaemophilic factor (recombinant) processed using a Plasma/Albumin-Free Method (rAHF-PFM) was first approved by the US FDA in July 2003 and subsequently, the EMA in 2004. It is available for clinical use in Taiwan since 2007.

Post-Authorisation Safety Surveillance (PASS) of factor VIII concentrates is essential in assessing adverse event incidence. This PASS project hence to assessed safety, efficacy, and immunogenicity of ADVATE in order to extend the clinical experience in Taiwan.

OBJECTIVES

•**Primary objectives** were to assess the incidence of non-serious and serious Adverse Events (AEs) that were at least possibly related to ADVATE (= sADR), including inhibitor formation, in subjects receiving ADVATE for either prophylaxis or on-demand treatment.

•**Secondary objectives** were to assess the haemostatic efficacy, number of ADVATE infusions required, and health-related quality of life in subjects receiving ADVATE.

METHODS

Key Inclusion Criteria

•Moderate or severe hemophilia A (baseline factor VIII ≤ 5%)

•Have been prescribed ADVATE

•Written informed consent

Key Exclusion Criteria

•Known hypersensitivity to the active substance or to any of the excipient

•Known allergic reaction to mouse or hamster proteins

Study Design

This was a prospective, uncontrolled, open-label, post-authorization safety surveillance. The surveillance followed a cohort design, and did not make binding stipulations on treatment or observation schedule.

Observation Period

12 months for each surveillance subject

Safety Assessment

•Incidence of serious and non-serious AEs at least possibly related to ADVATE

•For inhibitor analysis:

- It is recommended to test inhibitor every 4M.
- Inhibitors were categorized as either:
  - Low titer: 0.6 – 5 BU
  - High titer: > 5BU

Efficacy Assessment

- Clinical Assessment
- Overall efficacy of each bleed treatment was assessed by the treating physician, based upon review of the subject diary including infusion data and subject-rated face pain rating scale (Fig. 1) of individual bleed treatments at home, as well as subject clinical records, using a 4-point scale (Table 1)

Figure 1. Face Pain Rating Scale

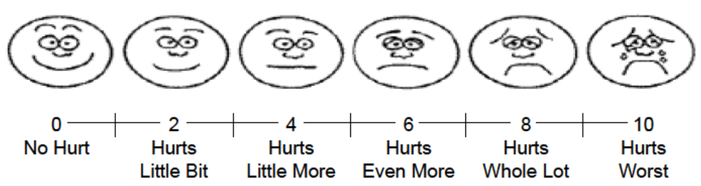

Table 1. Assessment criteria based on the changes of pain relief at 8-hr and 24-hr after 1st infusion

Time after 1st infusion	Changes of score	Rating
8-Hr	More than 4-point decrease of the score reaches 0	Excellent
	2-point or 3-point decrease	Good
	1-point decrease	Fair
	No change in score or worse	Poor
24-Hr	More than 5-point decrease of the score reaches 0	Excellent
	3-point or 4-point decrease	Good
	1-point or 2-point decrease	Fair
	No change in score or worse	Poor

- QoL: determined by employing the SF-36v2 questionnaires among subjects over the age of 12 years

RESULTS

Demographics

40 subjects were enrolled in this study, and all subjects completed 12M surveillance. (Table 2)

Table 2. Demographic Characteristics	N=40
Age (years)	
Mean (SD)	31.4 (14.5)
Median (Range)	31 (8~64)
Hemophilia A Severity	
Moderate	8 (20%)
Severe	32 (80%)
Baseline Factor VIII (%)	
Mean (SD)	1.15 (1.47)
Median (Range)	0.75 (0.0~7.7)
History	
History of factor VIII inhibitor	4 (10%)
Immune tolerance induction (ITI) therapy	2 (5%)
Subject s with Target Joints	27 (67.5%)
Single joint	11
Double joint	11
Triple joints	2
More than 3 joints	3

Table 3. Advate administration during surveillance period

Average duration	Mean	SD
Time on study (days)	379.4	29.2
Exact Exposure of ADVATE (days)	85.0	62.2
ADVATE prescription	**Numbers**	**%**
Prophylactic only	1	2.5
Prophylactic total	35	87.5
On-demand only	5	12.5
On-demand total	39	97.5
ADVATE for ITI therapy	2	5.0

Safety

•3 subjects (7.5%) reported a total of 5 SAE events, and 127 events of AE occurred in 35 subjects (87.5%)

•No AE or SAE was deemed related to ADVATE

•No fatal AE or death occurred during surveillance period

•Symptoms remained mostly mild and moderate in intensity and were resolved rapidly

•None of the study subjects was found to develop either high or low-titer Factor VIII inhibitor

Table 4. Adverse Event

Adverse Event (AE)	Number of events	Subject number (%)
Total number of AE happened	127	35 (87.5)
Intensity		
Mild	112	34 (85.0)
Moderate	10	5 (12.5)
Severe*	4	3 (7.5)
AE related to study drug	0	0
Serious Adverse Event (SAE)		
Total number of SAE happened	5	3 (7.5)
SAE related to study drug	0	0

* Out of 4 events of severe intensity, 3 were SAE

Efficacy

•A total of 1186 bleeding episodes occurred during the surveillance, out of which 1106 were spontaneous and 80 were caused by trauma. The most common bleeding sites were joints (84.5%) (Table 5)

•1-2 infusions of ADVATE controlled 92.9% of all bleeding episodes, 93.7% of spontaneous and 82.5% of bleeds due to trauma (Table 5)

•ADVATE was excellent or good to achieve haemostatic efficacy for 85.6% and fair in 12.6% of bleeding episodes at 24hr (Table 6)

•Overall there was no change in the subject reported SF-36v2 health-related quality of life during the study period

Table 5. New bleeding locations, causes, and number of infusions

Bleeding location	No. of occurrences	Cause of bleeding	
		Spontaneous	Trauma
Joints	1002 (84.5%)	955 (86.4%)	47 (58.8%)
Soft Tissue, Muscles	147 (12.4%)	124 (11.2%)	23 (28.8%)
Soft tissue, Other	37 (3.1%)	27 (2.4%)	10 (12.5%)
Total	**1186**	**1106**	**80**
Percentage	**100%**	**93.3%**	**6.7%**
Frequency of Advate Infusions for bleed resolution	**Number (%)**	**Number (%)**	**Number (%)**
1	937 (79.0%)	885 (80.0%)	52 (65.0%)
2	165 (13.9%)	151 (13.7%)	14 (17.5%)
More than 2	84 (7.1%)	70 (6.3%)	14 (17.5%)

Efficacy Assessment	8 hr	24 hr
Excellent	391 (33.0%)	857 (72.3%)
Good	404 (34.1%)	158 (13.3%)
Fair	324 (27.3%)	150 (12.6%)
Poor	67 (5.6%)	21 (1.8%)
Total	1186	1186

DISCUSSION AND CONCLUSION

•A large proportion of subjects had significant musculoskeletal disease at study start with 2/3 of subjects with target joint involvement, often multiple.

•Total number of new bleeds reported on average 30 by each patient. The higher bleeding number and target joint involvement showed that these 40 surveillance subjects were much more severe, compared to patients in the literatures [1,2,3,4].

•The differences in efficacy assessment scales and patient disease severity may contribute to the disparity of efficacy results of 95% excellent/good efficacy rating as described in the literature [2].

•In studies where comparable efficacy ratings were used, the efficacy assessment results were very similar [3, 4].

•Subjects with clinically significant abnormal ALT level (42.5%) were also positive for HCV antibody at baseline. None of HCV negative subjects demonstrated changes in ALT level during the surveillance period.

•ADVATE infusion was found to be safe in all 40 subjects with no related SAE, AE, or Factor VIII inhibitor development reported during the 1-year surveillance period.

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WFH2012
151--Tu
Outcome Assessment
Yeu-Chin Chen
DOI: 10.3252/pso.eu.WFH2012.2012
Poster presented at: WFH 2012 WORLD CONGRESS PARIS, FRANCE Sunday, July 8 - Thursday, July 12
PosterSessionOnline.com