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Inhibitors in previously treated patients: A review of the literature

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Abstract

Previously treated patients are the first patients to receive novel factor VIII products during clinical investigations under the rationale that a product with increased antigenicity is more likely to be detected in this population because of a low baseline risk of inhibitor formation compared to previously untreated patients. Since clinical investigations of factor products are not typically randomized comparisons, the rate of new inhibitor formation in a clinical trial is compared with the expected rates based on prior reports. The published experience of inhibitors in previously treated patients informs the number of new inhibitors per cohort that are acceptable in a clinical trial. However a single acceptable limit of new inhibitors fails to recognize the heterogeneity of inhibitors and their variable impact on clinical care. This review will discuss the published literature on epidemiology and clinical characteristics of inhibitors and possible risk factors for formation in previously treated patients.

Keywords

Hemophilia; inhibitor; previously treated patients; PTP

INTRODUCTION

As factor products containing novel expressions of the factor VIII (FVIII) gene are developed, a major concern is increased antigenicity leading to an anti-FVIII inhibitory antibody response. Accordingly, assessment of the risk of inhibitor formation is a major focus of the clinical development of novel FVIII products. In 1999, the International Society of Thrombosis and Haemostasis scientific subcommittee recommended the focused enrollment of previously treated patients (PTPs), defined as >150 lifetime exposure days, in initial clinical studies evaluating novel FVIII products [1]. This recommendation is based on the observed low rate of inhibitor formation after extensive exposure to FVIII which facilitates detection of inhibitor induction by the new factor product, presumably resulting from exposure of neo-epitopes on the novel FVIII product under investigation. Although the rate of new inhibitor formation after > 150 days is small, it is not zero, thus knowledge of

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the baseline rate of inhibitor formation in the PTP population is necessary to determine the upper acceptable limit of inhibitor development in clinical studies. Also important to this discussion is the clinical impact of new inhibitors in PTPs. Inhibitors that are limited in duration and do not require a change in the therapeutic approach to bleeding are the least clinically relevant, whereas those that are high responding, persistent, and increase the propensity to bleed are the most troublesome. In this report what is known about inhibitor formation in patients that have previously received FVIII will be reviewed.

EPIDEMIOLOGY

Despite the definition of PTP in 1999, the term has been used to represent patients with a variety of prior exposures to FVIII concentrates ranging from a single exposure day to >250 days of exposure. A lack of standardization of the term PTP has led many varied reports of the incidence of inhibitor formation in this population.

Surveillance studies at the time of product switch

Several reports have evaluated cohorts of patients switched from one product to another. Three such studies have identified markedly increased rates of inhibitor formation in PTPs. Following the introduction in 1990 of intermediate purity pasteurized FVIII concentrates in both Belgium and the Netherlands, the rate of inhibitor formation in PTPs (>200 lifetime exposure days) increased to 31 per 1,000 person years in Belgium and 20.1 per 1,000 person years in the Netherlands [2, 3]. In 1995 Bisinact was introduced in Belgium and although the incidence rate was not calculated, 8 out of 140 exposed patients with > 500 lifetime exposure days developed an inhibitor [4]. It has been hypothesized that the pasteurization process used with these preparations led to neo-epitopes thereby promoting inhibitor formation. These outbreaks demonstrated the vulnerability of patients exposed to neo-epitopes and highlight the need for assessment of inhibitor risk during evaluation of novel products.

More recently, two Canadian surveillance studies evaluated inhibitor formation following product changes [5, 6]. In the first study, 339 patients that were switched from plasma-derived to recombinant concentrates were monitored for 2 years. The incidence of inhibitor formation was found to be 2-3% (14.7 per 1,000 person years). This rate was thought to be similar to rates seen in Canada prior to the introduction of the recombinant product. A second study evaluated patients switching from Kogenate® to Kogenate® FS and did not find any inhibitors in the 185 subjects that were monitored for 2 years. Neither of these studies delineated the number of lifetime exposure days in the population and likely contained a spectrum of prior exposure. Nonetheless, new inhibitor formation was rare.

Treatment trials

In the pivotal trials leading to the licensure of the recombinant factor VIII products currently used in clinical practice, new inhibitor formation was rare occurring in 0-1.2% of the cohort under investigation (Table 1). If subjects had a history of an inhibitor or low titer at baseline, they were not considered to have a new inhibitor.

Post-marketing studies

Several studies have evaluated the use of recombinant FVIII concentrates following FDA licensure. During Recombinate's post-licensure period, 1993-2002, the annual incidence of new inhibitors in PTPs (> 50 lifetime exposure days) was 0.123% for all inhibitors and 0.0554% for high titer inhibitors [7]. In a small study evaluating patients who received Kogenate® over a one year period, no inhibitors developed 25 PTPs with > 50 lifetime exposure days [8]. In a retrospective review of 75 PTPs with >50 lifetime exposure days who were receiving Refacto®, 1 patient developed an inhibitor [9]. However, Roussel-Robert reported that 4 of 70 patients developed an inhibitor while receiving Refacto® [10]. Three of the 4 had >120 lifetime exposure days, and 1 had > 20 lifetime exposure days. During 18 months of post-licensure Advate use, 14 patients developed inhibitors. Eleven were documented to have < 50 lifetime exposure days and in 2 the amount of prior exposure was unknown. At least one patient had > 50 lifetime exposure days [11].

Cohort studies

Several cohort studies have been performed from which an incidence rate (number of new cases/population at risk x time which new cases were ascertained) of new inhibitor formation could be determined in the absence of new product exposure. In 1988 McMillan et al reported on a cohort of 1306 patients with hemophilia A during a 4 year multicenter study [12]. Overall, the rate of new inhibitor formation was 8 per 1,000 person years. Six inhibitors occurred in persons with > 150 lifetime exposure days and were detected on more than one occasion giving a rate of 1.55 per 1,000 person years in PTPs with >150 lifetime exposure days. Two additional inhibitors occurred in persons with 75 and 130 exposure days giving a rate of 2.06 per 1,000 person years in PTPs with >50 lifetime exposure days. The remaining 15 that were detected on more than one occasion occurred in patients with a median of 32 lifetime exposure days (range 8-48 days). Seven inhibitors were detected on only one occasion and occurred in patients with a median of 158 lifetime exposure days (range 45-250 days).

Ehrenforth et al evaluated subjects with moderate or severe hemophilia and found that 2 of 15 subjects that developed an inhibitor had more than 50 lifetime exposure days giving an incidence rate of 5 per 1,000 person years [13]. The remainder of subjects in that cohort had a median of 10 lifetime exposure days (range 4-34 days) prior to inhibitor formation. The UK Hemophilia Center Doctors' Organisation reported on the rate of inhibitor formation as a function of age [14]. Although they did not report the number of exposure days, those >15 years of age with severe disease are likely to be heavily pre-treated. Their rate of inhibitor development was 3.8 per 1,000 person years. This is substantially reduced from the rate of 34.4 per 1,000 person years in those < 5 years of age. More recently, analysis of the Centers for Disease Control and Prevention Universal Data Collection (UDC) Project determined the rate of new inhibitor formation in persons with hemophilia A that had been previously treated to be 2.14 per 1,000 person years [15]. Five of the seven new inhibitors occurred after >150 lifetime exposure days. The remaining two had 80 and 120 lifetime exposure days. A limitation of this study was the number of lifetime exposure days in the entire cohort could not be confirmed, however the observation that the inhibitors occurred only in those with > 80 lifetime exposure days suggests a heavily pre-treated cohort. From these cohort

studies we can conclude that inhibitor development can occur despite substantial prior exposure to factor concentrates even in the absence of exposure to neo-epitopes. However, it is an unusual event.

Inhibitor Characteristics

When new inhibitors developed during the 'outbreaks' in Belgium and Netherlands, the inhibitor was typically high titer but gradually declined after the patients were no longer exposed to the new products. Interestingly, the new inhibitors were detected after a relatively long duration, 98-170 days, of new product use during the first Belgium outbreak in 1993, whereas they occurred after 9-45 days in the second Belgium outbreak in 1995.

In the pivotal treatment trials, the inhibitor titer was variable. In the Kogenate® trial, the inhibitor was detected after 21 days of exposure to Kogenate® and the titer peaked at 28.5 BU/ml [16]. In the Refacto® trial, the inhibitor occurred after 107 exposure days to Refacto® and the titer peaked at 12.6 BU/ml 14 months after initial inhibitor detection [17]. In the Advate trial, a low titer inhibitor of 2.0 was detected after 26 days of exposure to Advate, however, 8 weeks later the inhibitor titer was negative despite continued exposure [18].

In the cohort study by McMillan et al, the median inhibitor titer in those with > 75 exposure days was 4.0 BU/ml (range 1.3-64 BU/ml). Four of the 9 had an inhibitor titer above 5 BU/ml [12]. Similarly, in the UDC study, the median was 2.0 BU/ml (range 1.1-47.5 BU/ml), and only one patient had a peak titer above 5 BU/ml [15]. The two subjects with an inhibitor after > 100 prior exposure days in the cohort reported by Ehrenforth et al had peak titers of 335 and 1070 BU/ml [13]. In a German registry, of the 11 patients with an inhibitor and >50 prior exposure days, 6 (54%) had a low responding inhibitor, though exact titers were not reported [19].

In the UDC study one of the 7 inhibitors lasted less than 6 months. Of those that lasted 6 months or longer, the mean duration was 1.7 years (95% CI 0.6-2.8 years) [15]. Two patients were treated with immune tolerance induction. Three patients had no change in their therapy despite identification of the inhibitor. Only one patient required a bypassing agent for treatment of bleeding, though three required increased dose of FVIII concentrates to treat bleeding.

The UDC study and cohort reported by McMillan included non-severe patients. Of the 7 patients with an inhibitor in the UDC cohort, 2 had non-severe disease [15]. In the McMillan cohort, 3 of 9 had non-severe disease [12]. The sample size of inhibitor patients in these cohorts is too small to determine if patients with non-severe disease are over represented.

Risk factors for inhibitor development

In the absence of exposure to a neo-epitope, as occurred in Belgium and Netherlands, what leads to inhibitor formation in patients with numerous days of exposure to FVIII concentrates is unknown. In the UDC study the sample size was too small to determine any statistically significant associations [15]. On univariate analysis there were trends for more inhibitor formation in those > 15 years of age compared with < 15 years of age and in those

receiving on-demand therapy compared with prophylaxis. No association was found with the type of therapy received.

Receiving factor replacement therapy by continuous infusion has been raised as a possible risk factor for new inhibitor formation. In a retrospective study that surveyed 13 German hemophilia treatment centers regarding the use of continuous infusion and inhibitor formation, they found that inhibitors developed in 10 patients that received continuous infusion for treatment of major bleeds and surgical procedures [20]. Of the 10 that developed an inhibitor, 3 had > 100 lifetime exposure days. Without knowing the frequency of inhibitors in those that did not receive continuous infusion, it is difficult to attribute the continuous infusion as a risk factor however, 30% of the inhibitors occurring in patients with > 100 lifetime exposure days is curious and deserves further investigation.

CONCLUSION

New inhibitor formation in persons with hemophilia A and > 150 lifetime exposures to FVIII concentrates is rare, occurring between 1.55 and 3.8 per 1,000 person years. Higher rates can occur when exposed to neo-epitopes as occurred with changes in the pasteurization process in the 1990s. Low titer inhibitors appear to be more likely; though a range of inhibitor titers have been reported. Why a failure of tolerance occurs in some heavily pre-treated patients and not others is unclear. Whether the risk increases with age and continuous infusion of factor concentrates and decreases with prophylaxis requires further investigation.

REFERENCES

1. White GC, DiMichele D, Mertens K, et al. Utilization of previously treated patients (PTPs), noninfected patients (NIPs), and previously untreated patients (PUPs) in the evaluation of new factor VIII and factor IX concentrates. Recommendation of the Scientific Subcommittee on Factor VIII and Factor IX of the Scientific and Standardization Committee of the International Society on Thrombosis and Haemostasis. *Thromb Haemost.* 1999; 81:462. [PubMed: 10102478]
2. Peerlinck K, Arnout J, Gilles JG, Saint-Remy JM, Vermeylen J. A higher than expected incidence of factor VIII inhibitors in multitransfused haemophilia A patients treated with an intermediate purity pasteurized factor VIII concentrate. *Thromb Haemost.* 1993; 69:115–8. [PubMed: 8456422]
3. Rosendaal FR, Nieuwenhuis HK, van den Berg HM, et al. Dutch Hemophilia Study Group. A sudden increase in factor VIII inhibitor development in multitransfused hemophilia A patients in The Netherlands. *Blood.* 1993; 81:2180–6. [PubMed: 8471777]
4. Peerlinck K, Arnout J, Di Giambattista M, et al. Factor VIII inhibitors in previously treated haemophilia A patients with a double virus-inactivated plasma derived factor VIII concentrate. *Thromb Haemost.* 1997; 77:80–6. [PubMed: 9031454]
5. Giles AR, Rivard GE, Teitel J, Walker I. Surveillance for factor VIII inhibitor development in the Canadian Hemophilia A population following the widespread introduction of recombinant factor VIII replacement therapy. *Transfusion science.* 1998; 19:139–48. [PubMed: 10187039]
6. Rubinger M, Lillicrap D, Rivard GE, et al. A prospective surveillance study of factor VIII inhibitor development in the Canadian haemophilia A population following the switch to a recombinant factor VIII product formulated with sucrose. *Haemophilia.* 2008; 14:281–6. [PubMed: 18194308]
7. Ewenstein BM, Gomperts ED, Pearson S, O'Banion ME. Inhibitor development in patients receiving recombinant factor VIII (Recombinate rAHF/Bioclone): a prospective pharmacovigilance study. *Haemophilia.* 2004; 10:491–8. [PubMed: 15357776]
8. Aygoren-Pursun E, Scharrer I, German Kogenate Study Group. A multicenter pharmacovigilance study for the evaluation of the efficacy and safety of recombinant factor VIII in the treatment of patients with hemophilia A. *Thromb Haemost.* 1997; 78:1352–6. [PubMed: 9408018]

9. Gringeri A, Tagliaferri A, Tagariello G, Morfini M, Santagostino E, Mannucci P. Efficacy and inhibitor development in previously treated patients with haemophilia A switched to a B domain-deleted recombinant factor VIII. *Br J Haematol*. 2004; 126:398–404. [PubMed: 15257713]
10. Roussel-Robert V, Torchet MF, Legrand F, Rothschild C, Stieltjes N. Factor VIII inhibitors development following introduction of B-domain-deleted recombinant factor VIII in four hemophilia A previously treated patients. *J Thromb Haemost*. 2003; 1:2450–1. [PubMed: 14629482]
11. Gomperts, ED. Advate inhibitor risk profile: 18 months post-licensure. In: Scharrer, I.; Wolfgang, S., editors. 35th Hemophilia Symposium 2004. Springer-Verlag; Hamburg: 2006. p. 38–41.
12. McMillan CW, Shapiro SS, Whitehurst D, Hoyer LW, Rao AV, Lazerson J. The natural history of factor VIII:C inhibitors in patients with hemophilia A: a national cooperative study. II. Observations on the initial development of factor VIII:C inhibitors. *Blood*. 1988; 71:344–8. [PubMed: 3122859]
13. Ehrenforth S, Kreuz W, Scharrer I, et al. Incidence of development of factor VIII and factor IX inhibitors in haemophiliacs. *Lancet*. 1992; 339:594–8. [PubMed: 1347102]
14. Darby SC, Keeling DM, Spooner RJ, et al. The incidence of factor VIII and factor IX inhibitors in the hemophilia population of the UK and their effect on subsequent mortality, 1977–99. *J Thromb Haemost*. 2004; 2:1047–54. [PubMed: 15219185]
15. Kempton CL, Soucie JM, Abshire TC. Incidence of inhibitors in a cohort of 838 males with hemophilia A previously treated with factor VIII concentrates. *J Thromb Haemost*. 2006; 4:2576–81. [PubMed: 17002659]
16. Schwartz RS, Abildgaard CF, Aledort LM, et al. Human recombinant DNA-derived antihemophilic factor (factor VIII) in the treatment of hemophilia A. recombinant Factor VIII Study Group. *The New England journal of medicine*. 1990; 323:1800–5. [PubMed: 2123300]
17. Courter SG, Bedrosian CL. Clinical evaluation of B-domain deleted recombinant factor VIII in previously treated patients. *Semin Hematol*. 2001; 38:44–51. [PubMed: 11449335]
18. Tarantino MD, Collins PW, Hay CR, et al. Clinical evaluation of an advanced category antihemophilic factor prepared using a plasma/albumin-free method: pharmacokinetics, efficacy, and safety in previously treated patients with haemophilia A. *Haemophilia*. 2004; 10:428–37. [PubMed: 15357767]
19. von Auer, C.; Oldenburg, J.; Krause, M.; Meisbach, W.; Scharrer, I. Inhibitors in PTP's: A Retrospective Study in Germany. In: Scharrer, I.; Wolfgang, S., editors. 35th Hemophilia Symposium 2004. Springer-Verlag; Hamburg: 2006.
20. von Auer C, Oldenburg J, von Depka M, et al. Inhibitor development in patients with hemophilia A after continuous infusion of FVIII concentrates. *Annals of the New York Academy of Sciences*. 2005; 1051:498–505. [PubMed: 16126990]
21. White GC 2nd, Courter S, Bray GL, Lee M, Gomperts ED. A multicenter study of recombinant factor VIII (Recombinate) in previously treated patients with hemophilia A. The Recombinate Previously Treated Patient Study Group. *Thromb Haemost*. 1997; 77:660–7. [PubMed: 9134639]
22. Abshire TC, Brackmann HH, Scharrer I, et al. Sucrose formulated recombinant human antihemophilic factor VIII is safe and efficacious for treatment of hemophilia A in home therapy-International Kogenate-FS Study Group. *Thromb Haemost*. 2000; 83:811–6. [PubMed: 10896230]

Table 1

Inhibitors in pivotal recombinant factor VIII clinical trials using PTPs as subjects

Product	N	PTP Definition	Baseline fVI II levels	No. of new inhibitors
Recombinate [21]	69	NR	5%	0
Kogenate® [16]	86	> 1 dose	NR	1
Kogenate-FS® [22]	73	100 ED	< 2%	0
Refacto® [17]	113	30 ED/yr	< 2%	1
Advate [18]	108	150 ED	< 1 %	1

PTP= previously treated

ED= exposure day

NR= not reported