Switching treatments in haemophilia: is there a risk of inhibitor development?

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Abstract

Patients with haemophilia A (and their physicians) may be reluctant to switch factor VIII (FVIII) concentrates, often due to concerns about increasing the risk of inhibitors; this reluctance to switch may contribute to patients missing the clinical benefits provided by the arrival of new factor VIII products. This topic was explored at the Eleventh Zürich Haemophilia Forum. Clinical scenarios for which product switching may be cause for concern were discussed; when there is a clinical need, there are no absolute contraindications to switching, but some patients (e.g. previously untreated patients and those undergoing elective surgery) may require more careful consideration. Both patient and physician surveys indicate that the reluctance to switch, and the fear of inhibitor development, does not appear to be evidence based. The evaluation of more recent data did not support previous studies suggesting that particular products (e.g. recombinant vs. plasma-derived and full length vs. B-domain modified) may be associated with increased risk. In addition, data from three national product switches showed that switching was not associated with increased inhibitor risk, but highlighted the need for regular inhibitor testing and for a centralised, unbiased database of inhibitor incidence. To conclude, current evidence does not suggest that switching products significantly influences inhibitor development.

Key words haemophilia; inhibitors; product switching

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The mainstay of treatment for haemophilia A is prophylactic and/or on-demand replacement therapy with plasma-derived (pd) or recombinant (r) factor VIII (FVIII) concentrates (1). When choosing between FVIII products, physicians must consider various factors, including safety, cost, and supply/availability. Changing the type of factor concentrate that patients use may be beneficial for a number of reasons. For example, new products may offer improved safety (e.g. lower risk of infection, fewer side effects), lower cost and more convenient product administration or storage, and may also have a longer product half-life, thereby enabling prophylaxis with fewer injections (2). Other reasons for switching products may be the arrival of a newer generation of the product, national contracting, patient/family preference and participation in clinical research (2).

Common treatment switches are from plasma-derived to recombinant products and from recombinant to different recombinant products. Switching treatments in this way is not a modern development. Indeed, it is rare for adult patients to have used the same factor concentrate through-
out their lives (2). However, there is often reluctance among both physicians and patients to switch treatments, largely due to the perception that switching treatments increases the risk of inhibitor development, which first arose from reports in the 1990s of increased inhibitor incidence following switches to pd-FVIII for which different viral-inactivation methods were used (3–5). However, this reluctance may not be in the best interest of the patient if there are otherwise good reasons to switch. Members of the Zürich Haemophilia Forum convened for their eleventh meeting in May 2013 to discuss treatment switching for patients with haemophilia A, focusing on the question of to what degree, if at all, switching increases the risk of inhibitor development. This report summarises our discussions and recommendations.

**Which patients may not be appropriate to switch?**

Most inhibitors occur at an early age and usually within the first 50 exposure days. As such, many physicians would prefer not to switch products during this time. However, it should be acknowledged that there are no clear data that demonstrate an increased risk of inhibitor when switching FVIII concentrate in patients prior to 50 exposure days.

Certain clinical scenarios have been associated with an increased risk of inhibitor development, and for some patients with haemophilia A, switching products requires careful consideration. Haemophilia patients with a history of inhibitors, including those in whom the inhibitor has been eradicated with immune tolerance induction (ITI), may relapse and constitute a group of individuals at higher risk of inhibitor development. There may be similar concerns for haemophilia patients with a family history of inhibitor and/or a higher risk mutation in the F8 gene. As such, there may be reluctance on the part of the physician and the patient to consider switching products when they have been shown to be tolerant of their current therapeutic product. If such individuals are to have the opportunity to benefit from advances in therapy such as those with increased safety profiles or extended duration of action, they would need to consider switching products. In this situation, it should be noted that there is no evidence of increased risk of inhibitor development (6).

Lastly, intensive treatment (including surgery) is reported to be associated with an increased risk of inhibitor development (7). As such, patients scheduled to have elective orthopaedic surgery should remain on their current product and switching in the intraoperative or early postoperative period should be avoided. However, for all patients, following discussions with patients or their caregivers, a product switch may be undertaken if there is a clinical need; there are no absolute contraindications for switching.

**Perceived barriers to switching treatment**

For patients for whom product switching may be appropriate, a reluctance to switch products may be associated with concerns regarding the potential negative outcomes of such a switch. In addition, some patients with haemophilia often develop a strong psychological link with their current product (2).

To investigate patient concerns regarding switching, a semi-structured, non-random, brief, online survey was conducted using the Web research platform SurveyMonkey®. Participants from seven national haemophilia organisations (Argentina, Brazil, Chile, Santo Domingo, Mexico, Nicaragua and Spain) were informally invited (by E.R.) through social media during 15 days in April 2013. Survey participation was voluntary and a total of 46 participants (of whom 27.5% were parents of a child with haemophilia) anonymously completed the online survey (response rate 85%). Ethical standards for online behavioural research were strictly followed and all participants gave their electronic consent before taking the survey. Data were provided regarding haemophilia A (n = 37) and B (n = 9), of which the majority of patients had severe haemophilia (n = 27), and some patients had been diagnosed with an inhibitor (n = 9). Of note, 57% of the respondents believed that the probability of inhibitor development was high or very high when switching product. Moreover, when asked to list up to five concerns related to switching product, inhibitor development appeared first in the list (25.3% of respondents), followed by potential product side effects (21.8%), product effectiveness (17.2%), safety/purity (17.2%), and finally, product quality and longevity (4.6%). Inhibitor development was therefore the greatest patient concern when considering switching treatments. The original survey and complete report in Spanish are available by email request to eduardo.remon@uam.es.

To explore concerns regarding product switching by healthcare professionals, a recently conducted DELPHI consensus exercise was undertaken to canvass expert opinion on the topic (6). Briefly, the DELPHI process is a structured group communication in which a complex problem is considered by a group of experts. The procedure usually begins with a face-to-face meeting to set the context of the communication, after which experts input their thoughts/opinions through several rounds of questions and answers. The DELPHI panel noted that currently available studies are often retrospective, characterised by a mixture of methodological approaches, and frequently lack appropriate control groups. Given this background, and the modest amount of data available on product switching, the DELPHI process provided an alternative approach to addressing the complex problem of assessing the risk of immunogenicity associated with product switching. The group addressed 14 separate items relating to the issue of product switching and the risk
of inhibitor development and reached a high level of consensus on most items. They, too, concluded that much of current clinical practice regarding treatment switching in haemophilia was not based on evidence, but on the fear of developing an inhibitor (6).

**Does product type influence the risk of inhibitor development?**

Treatment-related factors, including treatment intensity as briefly mentioned above, therapeutic regimen (i.e. prophylaxis vs. on-demand treatment) and product type have been proposed as possible influences on inhibitor development (7–12). For example, a systematic literature review concluded that inhibitor incidence was lower in patients treated with one pd-FVIII vs. those who had used multiple pd-FVIII concentrates or a single rFVIII product (12). Although a more recent systematic review using multi-way analysis of variance concluded that source of concentrate did not significantly influence inhibitor development (11), suggestions of an increased incidence of inhibitor development and treatment with rFVIII products, and also those with a B-domain deletion/modification, may continue to contribute to patient and physician reluctance to switch to new rFVIII products.

Three early studies in previously untreated patients (PUPs) suggested that the incidence of inhibitor development was less for those treated with pd-FVIII than in patients treated with rFVIII (13–15). However, significant differences in inhibitor development were only observed in two of these three studies (13, 14). In the UK study, inhibitors developed more frequently in patients initially treated with rFVIII when compared with pd-FVIII (P = 0.006) (13). In a French cohort study, the risk of inhibitor development was reported to be higher in patients treated with rFVIII than those treated with pd-FVIII, regardless of other risk factors (e.g. F8 genotype, history of inhibitors in patients with a family history of haemophilia, age at first FVIII infusion) (14). However, in Sweden, no significant increase in the incidence of inhibitors was reported for haemophilia A patients in the 1990s who were mainly treated with recombinant products (n = 10/48, total incidence 21%), as compared with the 1980s (n = 9/52, 17%), when patients received intermediate/high-purity plasma-derived concentrates (15).

The Concerted Action on Neutralising Antibodies in severe haemophilia A (CANAL) study was a retrospective, multi-centre cohort study designed to further describe the relationship between treatment and inhibitor development in 366 PUPs with severe haemophilia (residual FVIII activity <2%) born between 1990 and 2000 (9, 16). Data available on product type and inhibitor incidence from 316 PUPs were evaluated. A total of 82 patients (26%) developed clinically relevant inhibitors; of 181 patients first treated with rFVIII product, 53 (29%) developed inhibitors, while inhibitors were reported in 29 of the 135 (21%) patients treated with pd-FVIII, and the relative risk (RR) of inhibitors in pd-FVIII vs. rFVIII products was 0.8 (95% confidence interval [CI], 0.5–1.3) (16). In addition, switching between FVIII products did not appear to increase the risk of inhibitor development (RR, 1.1; CI, 0.6–1.6). Hence, the CANAL study results do not support previous findings suggesting an increased risk of inhibitor development with rFVIII products, nor that switching products may influence inhibitor development (16).

More recently, the potential influence of rFVIII vs. pd-FVIII product type on inhibitor development was also explored in the RODIN (Research Of Determinants of INhibitor development) study, which used data from the PedNet registry that comprised 29 centres in Europe, Canada and Israel. Data were evaluated from 574 PUPs born between 2000 and 2010. Inhibitory antibodies were reported in 177 children (cumulative inhibitor incidence, 32.4%). Overall, there was no difference in inhibitor risk between pd-FVIII and rFVIII products (adjusted hazard ratio 0.96; 95% CI, 0.62–1.49), and switching between different FVIII products was not associated with an increased risk of inhibitor development (adjusted hazard ratio 0.99; 95% CI, 0.63–1.56). However, a significantly increased risk of inhibitor development was found to be associated with second-generation (produced in baby hamster kidney [BHK] cells) vs. third-generation full-length rFVIII products (adjusted hazard ratio 1.60; 95% CI, 1.08–2.37) (7). Although this latter finding is intriguing, there is no clear biological explanation for the difference in inhibitor development between second- vs. third-generation full-length rFVIII.

Concerns regarding a potential increase in immunogenicity associated with B-domain deleted rFVIII were raised by an early Italian study of previously treated patients (PTPs) (17). Of 25 low-risk PTPs, one patient developed an inhibitor after switching from pd-FVIII to B-domain-deleted rFVIII (17). Results from a more recent meta-analysis by Aledort and colleagues of prospective clinical studies on product switching appeared to demonstrate an increased risk of inhibitor development with B-domain-deleted rFVIII in PTPs (8). However, “good results for meta-analyses come from inclusion of good data” (18), and in this respect, of the two studies that contributed the most to the final odds ratio for the Aledort meta-analysis, one consisted only of case reports (19) and the other contained only the prospective arm from the Italian study (17). Caution is therefore warranted when assessing the validity of these findings.

The ongoing European Haemophilia Safety Surveillance (EUNHASS), a prospective adverse event reporting system, is exploring the incidence of inhibitors in PUPs and PTPs and the potential factors that may be contributing to inhibitor development. Data reported from the first 2 years of the study, provided by 64 haemophilia centres from 27 European countries (caring for 22 242 patients), showed that the inhibitor rate in PUPs with severe haemophilia A was 25% overall, with a similar incidence of inhibitors in patients trea-
Inhibitor development in national product switches

To date, studies on three national product switches (Ireland, Canada and the UK) have been published (Table 1) (22–24). While all three studies examined product switching, the product switches were different, and only the UK study investigated inhibitor incidence in both switchers and non-switchers.

The national Irish product switch resulted from a national tender process in 2006 in which all patients with haemophilia A changed their FVIII treatment product en masse to a plasma and albumin-free recombinant full-length FVIII product (ADVATE®) (22). In this study, case records of Irish PTPs were retrospectively reviewed to evaluate the risk of inhibitor formation following this treatment switch. Only one of the 96 patients without a previous history of inhibitors developed an inhibitor following the switch. However, as this patient had only received three exposure days prior to the switch (22), the inhibitor might also have developed if the patient had remained on his previous treatment. In addition, there were no cases of recurrent inhibitor formation in any of 16 patients with previously documented inhibitors.

The Canadian national product switch surveillance study comprised 460 haemophilia A paediatric and adult patients from 17 Canadian comprehensive haemophilia care centres, of whom 274 had evaluable data (24). This study was conducted by the Inhibitor Subcommittee of the Association of Hemophilia Clinic Directors of Canada to evaluate inhibitor development in patients with haemophilia A following the switch to a second-generation rFVIII product (Table 1). An inhibitor was detected in four of the 274 (1.5%) evaluable patients at the time of the switch, but no additional patients with inhibitors were reported afterwards (24). This finding highlights the importance of studying patients prospectively and testing for inhibitors before and after switching.

A National Tendering Exercise conducted in the UK in 2009–2010 required half of patients receiving rFVIII to change rFVIII brands (23). Based on the contractual requirements of the exercise, patients were randomly selected for switching in each local treatment centre. Centres were requested to test all patients for inhibitors prior to the switching date and 6-monthly thereafter. A total of 1217 patients with severe haemophilia A lacking an inhibitor history were analysed; 535 patients switched rFVIII product and 682 patients did not. Almost all patients who switched changed to Refacto AF® (513/535). Four patients who

| Study          | Country | Switch to product | Population evaluated | Patients enrolled | Patients evaluated | Severe haemophilia A at baseline (preswitch) | Positive for inhibitors at baseline (preswitch) | Inhibitor detection at baseline (post-switch) |
|----------------|---------|-------------------|----------------------|-----------------|-------------------|---------------------------------------------|-----------------------------------------------|---------------------------------------------|
| Bacon et al. (22) | Ireland | ADVATE® | Switchers | 113 | 113 | 101 (89) | 2 (1.7) | 1 (0.9) |
| Rubinger et al. (24) | Canada | Kogenate® | Switchers | 460 | 274 | 220 (89) | 4 (1.5) | 4 (1.5) |
| Hay et al. (23) | UK     | ReFacto AF® | Switchers and non-switchers | 1217 | 535 | 1217 (100) | Non-switchers: 682 | Switchers: 4 (0.75) Non-switchers: 1 (0.1) |

NA, not applicable.

1One patient had previously documented inhibitors, and one child who had been on prophylaxis with Kogenate® developed an inhibitor during intense therapy for treatment of an acute bleed.

2Patients remaining on Kogenate®.

3The difference in inhibitor incidence rates between switchers and non-switchers was not significant ($P = 0.12$).
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switched, two from Kogenate® and two from ADVATE®, developed inhibitors; in two cases, the inhibitors were transient, while for the other two cases, patients were rapidly tolerised. The incidence of inhibitors reported (7.5/1000 treatment per years) did not significantly differ from the 5.31/1000 treatment year incidence observed during the 20-year period preceding the study ($P = 0.24$), although the study was underpowered. Of note, among the 682 non-switchers, one patient developed inhibitors.

As these three studies employed different methodologies and studied heterogeneous patient populations, the findings of each cannot be directly compared, nor can the data be pooled for a combined analysis. However, all three studies suggest that switching is not associated with an increased risk of inhibitor formation relative to the very low background frequency of immunogenicity of these products, although the results are not conclusive and should be interpreted with caution.

**Recommendations and future directions**

The implementation of prospective, controlled surveillance programmes on switching and not switching is imperative, as there is insufficient evidence currently available to support the development of clear “Best Practice” guidelines for switching. In addition, such surveillance programmes will provide researchers with the data needed to address the many unanswered questions regarding the patient-related and treatment-related factors that contribute to the risk of inhibitor development. Most importantly, for the full potential of surveillance programmes to be realised, all data on inhibitor development and products received should be submitted to a centralised, unbiased database to establish a baseline on the current inhibitor risk and include all new patients, regardless of which product they receive. This is the only way to ensure that the field is able to utilise all of the data in the service of our patients.

Given the limitations of the existing evidence base, we can make a number of recommendations for the conduct of future studies on product switching. First, inhibitor testing should be performed before and after the switch to determine if any new inhibitors detected may be in association with switching to the new treatment. Similarly, inhibitor testing should also be performed before and after intensive treatment/surgery.

Concerning routine patient care, educational materials addressing patients concerns about switching are needed because some of patients’ concerns are not supported by the actual evidence about the consequences of switching products. More importantly, physicians are encouraged to discuss directly with patients and parents their therapeutic approach and the other treatment options that are available before a more urgent need arises to consider switching. Doing so may increase patient satisfaction with treatment and foster more informed and positive attitudes when and if the need arises to address switching to a new product. In the future, it may become feasible in routine practice to calculate an inhibitor risk score and identify patients at high risk, thus aiding the evaluation of which patients to consider for switching treatments.

**Conclusions**

Among patients with haemophilia (and their physicians), there is often a reluctance to switch factor concentrates because of concerns about increasing the risk of inhibitors. However, current evidence does not suggest that switching products significantly influences inhibitor development. With the forthcoming arrival of new haemophilia treatments, a centralised database recording inhibitor development should be implemented as soon as possible.

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