The diffusion of recombinant Factor VIII: a study of physicians’ preference

Zwart-van Rijkom JEF (1,2), Plug I (3),
Rosendaal FR (3), Leufkens HGM (1), Broekmans AW (1)

(1) Department of Pharmacoepidemiology and Pharmacotherapy, Utrecht Institute for Pharmaceutical Sciences (UIPS), Utrecht, the Netherlands
(2) Institute for Medical Technology Assessment, Erasmus University Rotterdam, Rotterdam, the Netherlands
(3) Department of Clinical Epidemiology and Department of Hematology, Leiden University Medical Center, Leiden, the Netherlands

Submitted for publication
ABSTRACT

Aim and methods - The diffusion of recombinant Factor VIII (rFVIII) has been relatively slow in the Netherlands. In a previous study among hemophilia patients we found that physicians play an important part in the choice between plasma derived Factor VIII (pdFVIII) and rFVIII. The objective of the current study was to investigate the opinions of hemophilia treating physicians on this topic.

Results - On average, the physicians prescribed rFVIII to 56% of their patients. This percentage varied widely between centers. Only one doctor would choose to use pdFVIII if he would suffer from hemophilia A himself and 74% would choose to use rFVIII. Previously untreated patients were preferentially treated with rFVIII by 95% of the physicians, and young patients by 81%. HIV status, severity of the disease, prophylaxis, and type of product used by family members were no reasons for most physicians to change their advice.
INTRODUCTION
In 1995, recombinant Factor VIII (rFVIII) was introduced in the Netherlands for the treatment of patients with hemophilia A, as a possible substitute for plasma derived Factor VIII (pdFVIII). Now, six years later, rFVIII is used by about 50% of the Dutch patients, while the other 50% continue to use pdFVIII [1]. Compared to other biotechnology substitutions, the diffusion of rFVIII is relatively slow. In the Netherlands, both recombinant human growth hormone and recombinant human insulin quickly reached a complete replacement of their organic counterparts, and the recombinant follitropins have captured an 80% market share within 4 years [2-4]. Also in comparison to other countries, the diffusion of rFVIII in the Netherlands has been slow. Ireland, Scotland and Denmark have completely switched from plasma derived to rFVIII as a matter of health policy [5]. In France rFVIII represents 80% of all FVIII used [6], and in Germany it represents 50% [7].
In a previous study, we investigated determinants of the diffusion of rFVIII, by use of a postal questionnaire among Dutch hemophilia patients. We found that from 1995 onwards, nearly all children who had to be treated with FVIII for the first time (previously untreated patients, PUPs), were prescribed rFVIII. Older age, human immunodeficiency virus (HIV) positivity, infection with hepatitis C, and having family members who use pdFVIII, were negatively associated with switching from pdFVIII to rFVIII. A positive attitude towards innovations, a positive opinion on rFVIII, and having family members who use rFVIII, were positively associated with switching. In addition, there was a strong influence of the center in which patients were treated. The proportion of patients who had switched from pdFVIII to rFVIII varied from 0% to 100% in the small centers, and from 26% to 71% in the large centers. Only 21% of the patients considered themselves as the most influential person in choosing a certain type of clotting factor, while 54% considered their physician to be this person.
The objective of the current study was to investigate the opinions of hemophilia treating physicians on the choice between pdFVIII and rFVIII. The outcomes were compared with the outcomes from our previous study in patients.

METHODS
Mailing procedure
In May 2001, we sent a postal questionnaire to the 26 directors of the licensed hemophilia care centers in the Netherlands. Additional questionnaires were included, which they were asked to distribute among the colleagues in their department who autonomously treated hemophilia patients as well. To enable us to measure the response, we requested the directors to report to how many of their colleagues they had given a questionnaire. Reminders were sent after two weeks.
Content
The additional questionnaires for the colleagues were identical to the directors’ questionnaires, except that only the directors were asked to fill the characteristics of their department’s patient population: number of patients with hemophilia A and B, severity, number of patients on plasma derived and on recombinant clotting factors, number of patients with inhibitors and number of infections with HIV and hepatitis C.

The questionnaire for doctors was based on the questionnaire we developed for patients. To enhance comparability the following items have been copied from the patient’s questionnaire: aversion against switching, most important influence in clotting factor choice (physician himself, the patient, or both equally influential), preference for a specific producer (Dutch over foreign, not-for-profit over for-profit), and opinion on albumin-free formulations of recombinant Factor VIII. The items on aversion against switching were located at the beginning of the questionnaire, before the issue of recombinant versus plasma derived clotting factors was introduced. Also, we copied the question where, from a list of eight (price, effectiveness, user friendliness, producer’s image, knowledge on long-term effects, risk of infections, risk of product shortages and risk of inhibitor formation), respondents were asked to indicate which they found the five most important characteristics. Their opinion on the eight characteristics was asked on a 5-points scale (-2 very favourable for plasma, -1 favourable for plasma, 0 the same for plasma and recombinant, 1 favourable for recombinant, 2 very favourable for recombinant).

We also included specific questions on the personal characteristics of the responding doctor, such as age, sex, year of graduation from medical school, medical specialism, and whether they treated mainly adults, children, or both. In addition, the respondents were asked which type of clotting factor they would choose for themselves if they had severe hemophilia (plasma derived, recombinant or no preference). Before the questionnaire was actually sent out, two doctors were asked to complete the questionnaire and to give their comments. This ‘pilot’ was helpful in optimising the structure and the content of the questionnaire.

Analysis
To calculate the response, we assumed that directors who, after the reminder, did not respond to our questionnaire, had not distributed it among colleagues either. The departments were categorised into three groups: departments treating mainly adults, departments treating mainly children, and departments treating both. Personal characteristics of the respondents were described, as were the influences of patient characteristics on the doctor’s advice about rFVIII versus pdFVIII. The personal opinions of doctors on matters related to the choice between pdFVIII and rFVIII were described and were compared with the opinions patients expressed in our
previous study. Details about this study, including the mailing procedure and the content of the questionnaire, have been described in the previous chapter.

RESULTS

Response and participants

Eighteen directors returned the questionnaire (response 69%). They reported that they had forwarded the questionnaire to 18 colleagues. Overall, including colleagues, we received 30 filled-out questionnaires (response 30/44=68%). Together, the directors reported to take care of 1,316 patients with hemophilia A and 169 patients with hemophilia B. As such, our sample represents the treating physicians of >95% of all Dutch hemophilia patients. One director was excluded because he did not see hemophilia patients anymore. A total of 29 participating physicians, from 17 departments, remained for analysis.

Mean age of the respondents was 47 ± 3 years. Fifty-nine percent was male, and the average year of graduation from medical school was 1980. Seven percent (n=2) were MDs, 11% (n=3) internists, 46% (n=13) hematologists, 21% (n=6) pediatricians, and 14% (n=4) pediatric hematologists.

Departments

In total, the 17 departments took care of 1,236 FVIII users, 696 of which were using rFVIII (56%). However, this percentage varied widely between the departments. In the departments where they treated mainly adults (n=8; 501 patients), the proportion of patients using rFVIII ranged from 0 to 75% (median 12%), and in the departments where they treated mainly children (n=6; 167 patients), it varied between 0 and 100% (median 84%). On average the proportion of patients using rFVIII was 2.9 times higher in departments treating children than in departments treating adults (p=0.02).

Patient characteristics

Seventy percent of the 29 physicians indicated that they had discussed the choice between pdFVIII and rFVIII with all their patients. When asked on whose initiative their patients had generally switched from pdFVIII to rFVIII, 11% of the doctors answered that this had been on the initiative of the patient, 44% answered it was their own initiative (the physician’s), 30% answered that it varied, and 15% answered that none of their patients switched from pdFVIII to rFVIII. Only one respondent indicated the patient to be the most influential in choosing a FVIII product, 41% (n=11) indicated themselves (the physician), and 56% (n=15) said both were equally influential.
Table 1 To which patients do you tend to advise rFVIII instead of pdFVIII? Results are given in percentages (n=22).

<table>
<thead>
<tr>
<th>Patient characteristic</th>
<th>Doctor’s preference to advise rFVIII instead of pdFVIII</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Severity of the disease</strong></td>
<td></td>
</tr>
<tr>
<td>severe hemophiliacs</td>
<td>no preference</td>
</tr>
<tr>
<td>mild hemophiliacs</td>
<td></td>
</tr>
<tr>
<td><strong>Previously untreated patients (PUPs)</strong></td>
<td></td>
</tr>
<tr>
<td>PUPs</td>
<td>no preference</td>
</tr>
<tr>
<td>previously treated patients</td>
<td></td>
</tr>
<tr>
<td><strong>Age</strong></td>
<td></td>
</tr>
<tr>
<td>young patients</td>
<td>no preference</td>
</tr>
<tr>
<td>old patients</td>
<td></td>
</tr>
<tr>
<td><strong>HIV</strong></td>
<td></td>
</tr>
<tr>
<td>HIV positives</td>
<td>no preference</td>
</tr>
<tr>
<td>HIV negatives</td>
<td></td>
</tr>
<tr>
<td><strong>Prophylaxis</strong></td>
<td></td>
</tr>
<tr>
<td>patients on prophylaxis</td>
<td>no preference</td>
</tr>
<tr>
<td>patients not on prophylaxis</td>
<td></td>
</tr>
<tr>
<td><strong>Home treatment</strong></td>
<td></td>
</tr>
<tr>
<td>patients on home treatment</td>
<td>no preference</td>
</tr>
<tr>
<td>patients not on home treatment</td>
<td></td>
</tr>
<tr>
<td><strong>Family members using rFVIII</strong></td>
<td></td>
</tr>
<tr>
<td>patients with family members using rFVIII</td>
<td>no preference</td>
</tr>
<tr>
<td>patients without family members using rFVIII</td>
<td></td>
</tr>
<tr>
<td><strong>Compliance</strong></td>
<td></td>
</tr>
<tr>
<td>compliant patients</td>
<td>no preference</td>
</tr>
<tr>
<td>non-compliant patients</td>
<td></td>
</tr>
<tr>
<td><strong>Inquirement</strong></td>
<td></td>
</tr>
<tr>
<td>patients who do inquire about rFVIII</td>
<td>no preference</td>
</tr>
<tr>
<td>patients who do not inquire about rFVIII</td>
<td></td>
</tr>
<tr>
<td><strong>Fear for BSE</strong></td>
<td></td>
</tr>
<tr>
<td>patients afraid of BSE</td>
<td>no preference</td>
</tr>
<tr>
<td>patients not afraid of BSE</td>
<td></td>
</tr>
</tbody>
</table>

HIV=Human Immunodeficiency Virus, BSE=Bovine Spongiform Encephalopathy

Five doctors (17%) gave the same advice to all patients: one advised all his patients to use pdFVIII, two advised all their patients to use rFVIII, and two remained neutral and had their patients decide for themselves. The remaining 22 doctors gave differential advices. The reasons given for this were the limited availability of rFVIII (23%), differences between patients (32%), or both (46%). The 22 doctors who gave differential advices were asked to which patients they tended to advise rFVIII instead of pdFVIII. The results are shown in Table 1.
Young patients were preferentially treated with rFVIII by 81% of the respondents, and PUPs by 95%. Thirty percent preferred to give rFVIII to HIV negative patients. Twenty-nine percent of the doctors were more inclined to advise rFVIII to patients who were afraid of BSE than to patients who were not afraid of BSE. Twenty-four percent took in consideration whether family members of the patient were already using rFVIII.

**Opinions**

Figure 1 shows how doctors and patients rated the importance of the eight predefined product characteristics in choosing between different clotting factor products. The average rating for a product characteristic could be 5 at the most and 0 at the least. Risk of infections and knowledge on long-term effects were the most important characteristic. Risk of product shortages and of inhibitor development ranked number 3 and 4.

With regard to the transmission of infections, most doctors believed that the risk is greater with pdFVIII as compared to rFVIII (Figure 2A). However, knowledge on long-term effects is better on pdFVIII, was the opinion of the majority of the physicians (Figure 2B). All doctors were of the opinion that rFVIII and pdFVIII are equally effective. Also on the topics of inhibitor formation (Figure 2C), user friendliness, and producer’s image, doctors did not see a difference between pdFVIII and rFVIII. As can be seen in Figure 2D, opinions on the risk of product shortages were very much divided. The summarised score for the physicians’ opinions on product characteristics was -0.6 (95% CI -2.0 – 0.1). If the doctors would suffer from severe hemophilia A themselves, 74% would choose to use rFVIII, 4% pdFVIII, and 22% had no preference.

Most doctors neither agreed nor disagreed with the statement ‘I prefer to use FVIII from a Dutch producer over FVIII from a foreign producer’ (Figure 2E). The physicians were either neutral or had a preference for a not-for-profit provider (Figure 2F). With the statement ‘Switching from one clotting factor product to another may cause problems’, most doctors (48%) disagreed (Figure 2G). With the statement ‘If you are doing well with your current treatment, you should never change to another clotting factor product’ (the notion to never change a winning team), 38% of the doctors (Figure 2H).

In 2000, two virtually albumin-free formulations of rFVIII (Kogenate Bayer® and Helixate NexGen®) were introduced. They contain 1000 times less plasma derived albumin than the former formulations, and have an additional detergent based purification step, further reducing the potential for virus transmission [8]. Twenty-six of the 29 doctors (90%) knew about the introduction of albumin-free formulations of rFVIII.
Twenty-one considered it an improvement (81%), while 5 thought it made no difference. The introduction of albumin-free formulations of rFVIII did not influence the policy of 89% of the doctors; only 11% started to prescribe more rFVIII.

**DISCUSSION**

On average, the physicians prescribed rFVIII to 56% of their patients. This percentage varied tremendously between departments, both within the group of departments treating mainly children, as well as within the group of departments treating mainly adults. Unfortunately, the number of departments was too small to use multiple linear regression and to investigate whether the opinions or the innovativeness of the physicians within a department were predictive of the proportion of patients on rFVIII.

According to expectations, PUPs were preferentially treated with rFVIII by 95% of the physicians. In the study among patients we found that, even when PUPs were excluded, people of younger age were more likely to have switched from pdFVIII to rFVIII than people of older age. Here, 81% of the physicians confirmed that they tend to advise rFVIII more often to younger patients than to older patients. As a result, the proportion of patients using rFVIII was on average 2.9 times higher in departments treating mainly children than in children treating mainly adults. In our study among patients HIV positivity was negatively associated with switching from pdFVIII to rFVIII.
Figure 2: Opinions of doctors and patients on various topics

**Figure 2a** Risk of infections

- Much larger for plasma:Doctors - Patients
- Larger for plasma:Doctors - Patients
- Equal:Doctors - Patients
- Larger for recombinant:Doctors - Patients
- Much larger for recombinant:Doctors - Patients

**Figure 2b** Knowledge on long-term effects

- Recombinant much better:Doctors - Patients
- Recombinant better:Doctors - Patients
- Equal:Doctors - Patients
- Plasma better:Doctors - Patients
- Plasma much better:Doctors - Patients

**Figure 2c** Risk of inhibitor formation

- Much larger for plasma:Doctors - Patients
- Larger for plasma:Doctors - Patients
- Equal:Doctors - Patients
- Larger for recombinant:Doctors - Patients
- Much larger for recombinant:Doctors - Patients

**Figure 2d** Risk of product shortages

- Much larger for plasma:Doctors - Patients
- Larger for plasma:Doctors - Patients
- Equal:Doctors - Patients
- Larger for recombinant:Doctors - Patients
- Much larger for recombinant:Doctors - Patients

**Figure 2e** I prefer a Dutch producer over a foreign producer

- Strongly agree:Doctors - Patients
- Agree:Doctors - Patients
- Neutral:Doctors - Patients
- Disagree:Doctors - Patients
- Strongly disagree:Doctors - Patients

**Figure 2f** I prefer a not-for-profit over a for-profit producer

- Strongly agree:Doctors - Patients
- Agree:Doctors - Patients
- Neutral:Doctors - Patients
- Disagree:Doctors - Patients
- Strongly disagree:Doctors - Patients

**Figure 2g** Switching may cause problems, e.g. inhibitor formation

- Strongly agree:Doctors - Patients
- Agree:Doctors - Patients
- Neutral:Doctors - Patients
- Disagree:Doctors - Patients
- Strongly disagree:Doctors - Patients

**Figure 2h** ‘Never change a winning team’

- Strongly agree:Doctors - Patients
- Agree:Doctors - Patients
- Neutral:Doctors - Patients
- Disagree:Doctors - Patients
- Strongly disagree:Doctors - Patients
The current study among physicians showed that for most doctors HIV positivity was not a reason to advise pdFVIII. Therefore, the association must go largely through patient preferences. Similarly, the influence of the product choice of family members must be explained by patients’ preferences, as only 24% of the doctors’ indicated that this was a reason for them to adjust their advice.

The doctors’ ranking of the importance of eight predefined product characteristics was quite similar to that of the patients. On average, the doctors valued the difference in risk of infections between rFVIII and pdFVIII as smaller than the patients did. Also, the knowledge on long-term effects and the risk of product shortages were assessed more in favour of pdFVIII by doctors than by patients.

Overall, doctors were less in favour of rFVIII than patients were (summarised score -0.6 versus 3.0). Still, if they had suffered from hemophilia A themselves, only one doctor would choose to use pdFVIII, and 74% would choose to use rFVIII.

Sixty-eight percent of the 22 doctors who gave different advices to different patients, indicated that they did so, among other things, because of the limited availability of rFVIII. In the preparatory interviews, which we conducted to construct the questionnaire for patients, we learned that the hemophilia treating physicians, united in the Dutch Hemophilia Treatment Society, had agreed upon the launch of rFVIII to introduce this new product very gradually to build up experience and to minimise the risk of shortages. They reasoned that a sudden and complete switch to rFVIII, would mean the end of the production of pdFVIII by the Central Laboratory of the Netherlands Red Cross Blood Transfusion Service (CLB), the major provider of plasma derived FVIII (pdFVIII) in the Netherlands. They preferred to keep both the CLB and the producers of rFVIII into business, as history had learned that dependence on a single producer makes one vulnerable. It turns out that physicians have indeed adhered to this agreement.

In conclusion, the decision of physicians united in the Dutch Hemophilia Treatment Society to introduce rFVIII only gradually has greatly influenced the diffusion of rFVIII in the Netherlands. The physicians decided to preferentially prescribe rFVIII to all PUPs, and this agreement was largely followed. Beside this, they left room to switch some, but not all patients from pdFVIII to rFVIII. Only in this part patient preferences do come into play.

ACKNOWLEDGEMENTS
The authors want to thank Marjolein Peters and Marijke van den Berg for their critical appraisal of the questionnaire. In addition, we thank the Dutch Hemophilia Treatment Society for their kind co-operation with the conduct of this study.
REFERENCES

5. Source: Plasma Protein Therapeutics Association (PPTA Europe).
7. Source: Deutsche Hämophiliegesellschaft zur Bekämpfung von Blutungskrankheiten.