

LETTER TO THE EDITOR

International survey of attitudes towards secondary prophylaxis with recombinant factor VIIa in haemophilia A patients with inhibitors

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Primary prophylaxis with factor concentrates benefits patients with severe haemophilia who do not have inhibitors, through the decreased frequency of bleeding and the prevention of joint damage [1,2]. Although prophylaxis with concentrates of the deficient factor is precluded in haemophilia patients with high-responding inhibitors, the prophylactic use of bypassing agents may be considered as a therapeutic option, particularly after the report of the first prospective randomized clinical trial conducted to evaluate a bypassing agent for secondary prophylaxis in haemophilia patients with inhibitors and high requirements for on-demand therapy [3,4]. In this trial, 22 patients with haemophilia A or B and inhibitors who had experienced ≥ 4 bleeds in the previous month received 3 months of daily prophylaxis with recombinant activated factor VII (rFVIIa, NovoSeven®; Novo Nordisk, Bagsvaerd, Denmark), at a dose of either 90 or 270 $\mu\text{g kg}^{-1}$, after which they had a 3-month post-prophylaxis follow-up. During prophylaxis, bleeding frequency was significantly ($P < 0.0001$) reduced compared with the pre-prophylaxis period (by 45% and 59% for patients receiving 90 or 270 $\mu\text{g kg}^{-1}$, respectively). No thromboembolic or other adverse events were observed. Unexpectedly, the majority of the reduction in bleeding frequency was maintained during the 3-month post-prophylactic follow-up [27% ($P < 0.01$) and 50% ($P < 0.0001$) reductions vs. pre-prophylaxis for the rFVIIa 90 or 270 $\mu\text{g kg}^{-1}$ dosages, respectively] [3]. Compared with the pre-prophylaxis period, during prophylaxis patients had significant reductions in the proportion of days spent in hospital (13.5 vs. 5.9%; $P < 0.01$) and

for which they were absent from work/school (38.7% vs. 16.7%; $P < 0.05$) [3,4]. Health-related quality of life tended to improve both during and after rFVIIa prophylaxis [4].

With these results as background, we chose to determine the prevailing attitudes towards secondary prophylaxis for haemophilia patients with inhibitors, through a survey conducted interviewing physicians from haemophilia centres and healthcare providers in Europe and the USA.

Survey methodology

Fifty-one interviews were conducted in five large countries (France, Italy, Spain, UK and USA) between July and September 2007 by a consultancy agency that was contracted by Novo Nordisk to carry out the survey. Results were analyzed independently from the sponsor. A total of 31 interviews were performed with physicians (5, 5, 1, 6 and 14 interviews in France, Italy, Spain, UK and USA) and 20 interviews with providers (2, 2, 1, 6 and 9 interviews in France, Italy, Spain, UK and USA). Depending on the country involved, providers included national payers, hospital pharmacists from major haemophilia centres, managed care organizations and Medicaid (a federal-state entitlement programme for citizens of USA with low incomes). Interviewees were shown a summary of the results of the aforementioned clinical trial. They were also given a handout showing cost calculations for on-demand and secondary prophylactic therapy specific for their country and were asked a series of questions. Qualitative analyses of the responses were subsequently performed, and weighted according to the number of haemophilia patients in each country.

Survey results are shown in the Table 1. The main unmet need in the treatment of patients with inhibitors was considered more effective secondary prophylaxis,

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Table 1. Main survey results.

	Physicians (<i>n</i> = 31), %*	Healthcare providers (<i>n</i> = 20), %*
Main unmet medical need in the treatment of inhibitor patients		
Efficacious and cost-effective secondary prophylaxis	57	56
Attitude towards secondary prophylaxis		
Positive	52	44
Indifferent	32	56
Negative	16	0
Advantages of rFVIIa prophylaxis compared to on-demand treatment		
Reduction in bleeding frequency	75	67
Reduction in hospital days and time absent from work/school	5	25
Disadvantages of rFVIIa prophylaxis compared with on-demand treatment		
Treatment costs	36	17
Need for daily injections	15	20
Inhibitor patients considered suitable for prophylaxis		
High bleeding frequency	74	88
Severe bleeds (e.g. intracranial bleeding)	57	18
Young patients	45	18
Respondents who consider rFVIIa secondary prophylaxis a desirable treatment option	90	94

*Percentage mentioning the listed attribute, weighted according to the number of haemophilia patients in each country, based on prevalence rates. This does not necessarily total 100% in all categories, as only the key results are shown.

that had also to be cost-effective. In general, the interviewees had a positive attitude towards prophylaxis, and there was more support for secondary prophylaxis in children than in adults. Indeed, the reported suitability of patients for this mode of treatment delivery was strongly dependent upon the age of the patients, as well as on the frequency and severity of bleeding. The interviewees believed bleeding frequency to be the most important of these criteria, although the perception of the minimum number of monthly bleeding episodes necessary for the implementation of prophylaxis varied among the respondents. The severity of bleeding episodes was an additional strong argument for prophylaxis, more for physicians than for providers. Although the numbers are too small to firmly establish this, there was no evidence that the origin of the providers and physicians (USA vs. non-USA) and the size of the haemophilia centre (including number of inhibitor patients) affected the pattern of responses.

The interviewees considered the key advantage of rFVIIa secondary prophylaxis compared with on-demand treatment to be the reduction in the number of bleeds. Healthcare providers particularly appreciated the positive impact of prophylaxis on the reduction in the proportion of days of hospitalization and the decrease in the amount of time for which patients were absent from work/school. As expected, the cost of the secondary prophylactic regimen was mentioned as the main hurdle. Some interviewees also cited the need for daily injections, or mentioned that they would have hoped for an even greater reduction in bleeding than was evident from the clinical trial.

Overall, rFVIIa secondary prophylaxis was considered a desirable option by 90% of the respondent physicians and 94% of the providers. Almost 80% of the physicians interviewed in the survey envisaged using secondary prophylaxis. Selected patients were cited as those with frequent or severe/life-threatening bleeds, or those who had high on-demand costs. A majority of the interviewees would fund, or argue for the funding of, prophylaxis in children or patients with frequent bleeds. Lower body weight, the corresponding lower required dosage of rFVIIa, and hence the lower cost involved, were important determinants of the preference for small children as a target for prophylaxis.

Conclusions

Currently, the main therapeutic goal in haemophilia patients with inhibitors is effective on-demand therapy for bleeding, with medication that can be administered early and at home. In Europe, a single dose of rFVIIa 270 µg kg⁻¹ has recently been approved for the treatment of mild to moderate bleeds in such patients. This new therapeutic regimen facilitates early treatment of bleeding episodes, which can take place in patients' homes.

The data from a clinical trial [3,4] provide preliminary evidence of the efficacy and safety of rFVIIa in secondary prophylaxis, while the similar reductions in bleeding frequency during prophylaxis for patients who received rFVIIa 90 or 270 µg kg⁻¹ suggest obvious advantages in terms of cost for the lower dose. Larger similar trials are warranted to

provide additional information on prophylaxis in haemophilia patients with inhibitors.

Disclosures

One of the authors (PAPdM) is employed by Novo Nordisk. PMM is acting as a consultant for Novo Nordisk and has received fees as a speaker.

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