

LETTER TO THE EDITOR

Assessing patient and caregiver preferences for treatment of haemophilia A: A discrete choice experiment

Dear Editor,

The primary goal of treatment of persons with haemophilia A (PwHA) is prevention or reduction of bleeding events; other goals are pain reduction, joint damage and disability and to improve quality of life (QoL).¹ Standard of care for PwHA without inhibitors in those with severe disease has long been prophylactic intravenous infusions of factor VIII (FVIII) replacement. New treatment options have become available in recent years, including extended half-life factor- and non-factor-based therapies. The different treatments available have a variety of characteristics. For example, the burden of standard half-life FVIII infusions two or three times per week is higher than for less frequent administration of extended half-life FVIII therapies, which can affect patient acceptance and QoL.^{2,3} Other treatment options include non-factor therapies that are administered subcutaneously and mimic the clotting activity of FVIII. One such therapy is emicizumab, which is approved for prophylaxis to prevent or reduce the frequency of bleeding episodes in adults and children with haemophilia A with or without FVIII inhibitors.⁴ Emicizumab can be administered once per week, every 2 weeks or every 4 weeks, is associated with a lower bleed rate than FVIII prophylaxis⁵ and improves physical health-related QoL compared with no prophylaxis.⁶

There is little evidence on which treatment characteristics, or 'attributes', matter most to PwHA without inhibitors and to their caregivers. To assess these preferences, especially in situations where out-of-pocket (OOP) costs (i.e., the expenses that insured persons must themselves pay to healthcare providers) vary widely between treatment types, we conducted a discrete choice experiment (DCE) in line with recommendations by the International Society of Pharmacoeconomics and Outcomes Research (ISPOR).⁷ Our study focused on haemophilia A without current FVIII inhibitors. Although previous DCEs have examined treatment preferences of PwHA,⁸⁻¹⁰ those studies did not investigate some of the important attributes that may differentiate between factor and non-factor therapies, such as frequency and method of administration for all currently available treatment options.

Treatment attributes for potential inclusion in the DCE were identified through a literature review. These were evaluated by a

team of experts, including haematologists, a haematological nurse and outcomes researchers, who developed a shortlist of 13 attributes in six categories to be included in a pre-test survey.

Participants in the pre-test survey, who were three PwHA (≥ 12 years of age, without current FVIII inhibitors) and three caregivers of PwHA without inhibitors, were asked whether each attribute was relevant and written clearly and whether attribute levels were within the usual range, in their experience. Based on the results of the pre-test survey and to reduce the cognitive burden for participants, the number of attributes included in the final survey was decreased to eight. These related to efficacy, safety, administration, QoL, emergency treatment and cost and consisted of 36 choice sets (18 without and 18 with the OOP cost attribute).

Inclusion criteria for participants in the final survey were the same as for pre-test survey. Participants were enrolled during their regular visits to haemophilia clinics at The Louisiana Center for Bleeding and Clotting Disorders at Tulane University School of Medicine, New Orleans, LA, USA or Washington Center for Bleeding Disorders at Bloodworks Northwest, Seattle, WA, USA. Key demographic and clinical characteristics of the 101 included study participants are presented in Table 1. Each participant received a US\$25 gift card incentive. This study was approved by Tulane University Human Research Protection Institutional Review Board Office and at Bloodworks through the commercial Western Institutional Review Board.

Participants completed the survey either during their clinic visit or remotely via a web link. As with the pre-test survey, the final survey was in a question-answer format, with full profiles presented for each treatment scenario. Participants were asked to choose between multiple sets of pairs of hypothetical treatments. Treatment profiles were presented without and then with the OOP cost attribute because it was thought that OOP costs may dominate the participants' preferences. OOP costs are difficult to estimate but insights gained during pre-testing suggested that the levels presented in the survey were reasonable.

Responses were analysed in conditional logistic models to estimate relative preference weights of treatment attributes and willingness to pay and were fitted without and then with OOP costs. Fitting a model excluding OOP costs allowed the preferences of

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TABLE 1 Demographic and clinical characteristics of study participants

Characteristic	Adult PwHA (n = 65)	Paediatric PwHA (n = 36) ^a
Age, years, mean (SD)	35.1 (12.7)	10.5 (4.1)
Male, n (%) ^b	65 (100.0)	36 (100.0)
Race, n (%) ^c		
White	45 (69.2)	27 (75.0)
Black	6 (9.2)	5 (13.9)
Asian	6 (9.2)	2 (5.6)
Health insurance, n (%) ^c		
Private ^d	49 (75.4)	16 (44.4)
Public ^e	12 (18.5)	17 (47.2)
None	3 (4.6)	0 (0.0)
Disease severity, n (%) ^{c,f}		
Mild	19 (29.2)	12 (33.3)
Moderate	10 (15.4)	2 (5.6)
Severe	36 (55.4)	21 (58.3)
Annual bleed rate, n (%) ^b		
1–3 bleeds	28 (43.1)	18 (50.0)
4–6 bleeds	8 (12.3)	6 (16.7)
>6 bleeds	17 (26.2)	2 (5.6)
None	11 (16.9)	10 (27.8)
Past FVIII inhibitors, n (%) ^g	8 (12.3)	5 (13.9)
Current treatment (at time of consent), n (%) ^h		
On demand	31 (47.7)	16 (44.4)
Prophylaxis	41 (63.1)	24 (66.7)
Other	3 (4.6)	2 (5.6)
None	3 (4.6)	1 (2.8)
Type of treatment (at time of consent), n (%) ^h		
Bypassing concentrates	3 (4.6)	2 (5.6)
Short-acting FVIII	35 (53.8)	16 (44.4)
Long-acting FVIII	20 (30.8)	13 (36.1)
Non-factor products (e.g., emicizumab)	3 (4.6)	7 (19.4)
Other products (e.g., stimate)	4 (6.2)	8 (22.2)
None	7 (10.8)	0 (0.0)
Frequency of treatment (at time of consent), n (%)		
On demand	3 (4.6)	4 (11.1)
Once every 2 weeks	3 (4.6)	0 (0.0)
Once a week	3 (4.6)	7 (19.4)
Twice a week	3 (4.6)	2 (5.6)
A few times a week	32 (49.2)	16 (44.4)
Daily	1 (1.5)	0 (0.0)
Did not answer this question	17 (26.2)	7 (19.4)
Previous/current use of central device, n (%)	23 (35.4)	16 (44.4)

Abbreviations: FVIII, factor VIII; PwHA, persons with haemophilia A; SD, standard deviation.

^aFive of the 36 children with haemophilia A, who were aged 12–17 years, completed their own survey; for the remaining 31 children, the survey was completed by caregivers. The mean age of the caregivers who participated was 38.9 (SD, 7.6) years.

^bAll persons with haemophilia A included in this study were male, reflecting the genetic aetiology of the disease.

^cRemaining persons with haemophilia A responded "Other"/"Don't know"/"Prefer not to answer".

^dIncludes employer/group-sponsored or individual commercial insurance plans.

^eIncludes Medicare, Medicaid or other federal insurance.

^fSeverity levels defined by FVIII levels in the blood: mild, 6–40%; moderate, 1–5%; and severe, <1%.

^gNo participant had FVIII inhibitors at the time of this study.

^hParticipants could report more than one option.

non-cost-related attributes to be examined without the influence of OOP costs, whereas fitting an additional model including OOP costs acted as a sensitivity analysis to examine the extent to which OOP costs influenced the preference weights of other treatment attributes. In the latter model, OOP costs were included as a continuous variable. Subgroup analyses, based on age of PwHA (adult/paediatric), disease severity (mild/moderate/severe) and current treatment (short-acting FVIII/long-acting FVIII/non-factor), were conducted in models excluding OOP costs. Finally, willingness-to-pay values were computed using the results of the model with OOP costs included. Willingness to pay was calculated for each treatment attribute level that was significant in the model, by dividing the model coefficient (relative preference weight) of the attribute level by the negative model coefficient of the OOP cost.

When OOP costs were excluded from consideration, all treatment attributes were found to be associated with statistically significant odds ratios when comparing at least one level of that attribute with the reference level (Figure 1). The clearest preference was for low risk of thromboembolic events or other side effects, indicating that this was the most influential attribute: PwHA and caregivers

are more than three times as likely to choose a treatment with a low risk than one with a high risk. PwHA and caregivers also significantly preferred the following: none or 1–2 annual bleeding events versus 5 or more annual bleeds; low risk of inhibitor development versus high risk; treatment administered once every 2 weeks or every 4 weeks versus a few times a week; treatment administered subcutaneously versus intravenously; high ability to perform normal activities without bodily pain or fear of bleeding versus low ability; and treatments that can be used for both preventing bleeds and treating emergency bleeds versus treatments that do not do both of these things. The least preferred attribute versus a reference level was administration via port infusion. The results were similar when OOP costs were included in the regression model. For each US\$10 per month increase in OOP costs, PwHA and caregivers were significantly less likely to prefer the treatment (odds ratio, [95% confidence interval], 0.96 [0.96, 0.97]).

Results of subgroup analyses were largely in line with the results from the overall sample. However, although the small sample sizes for some subgroups mean that the results should be interpreted with caution, several differences are notable. For example,

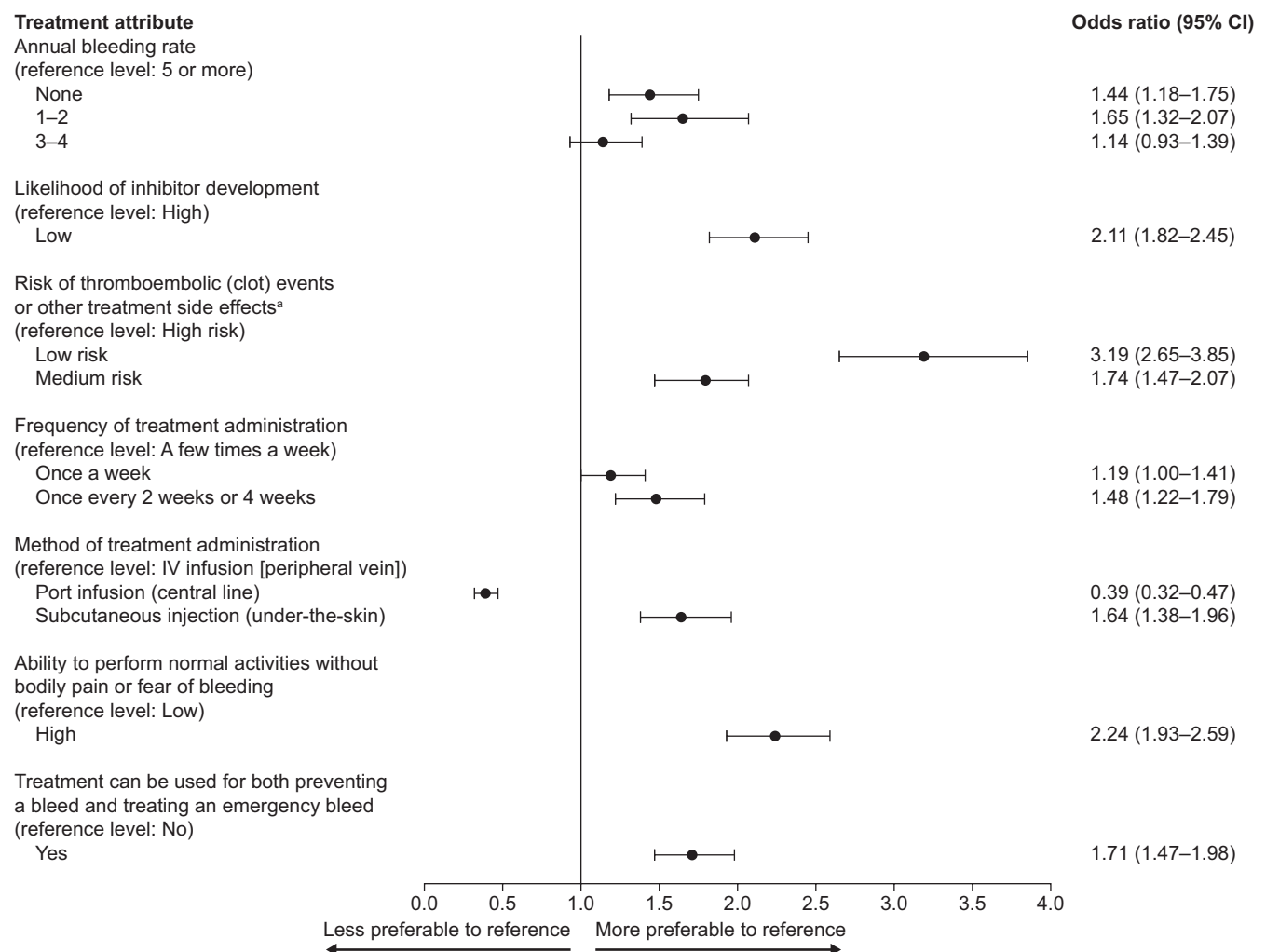


FIGURE 1 Odds ratios for preference for treatment attributes and levels, excluding out-of-pocket costs. CI, confidence interval; IV, intravenous.^aFor simplicity and clarity, arbitrary values were used to quantify risk levels

in children with haemophilia A, there was a significant difference in preference between 3–4 annual bleeds and 5 or more annual bleeds (odds ratio, [95% confidence interval], 1.53 [1.10, 2.14]), in addition to significant differences in preference between none (2.31 [1.65, 3.22]) or 1–2 annual bleeds (2.39 [1.63, 3.51]) and 5 or more annual bleeds. In PwHA with moderately severe haemophilia A, there was no significant difference in treatment preference between levels of annual bleeding rate. Frequency of administration was not a significant treatment attribute in children with haemophilia A, PwHA with mild disease and PwHA currently treated with long-acting FVIII or non-factor therapies.

Of the attributes for which statistically significant results were observed in the overall sample, the largest willingness-to-pay amount was US\$365.83 per month. PwHA and caregivers from the two included treatment centres in the USA were willing to pay that amount to switch from a treatment with high risk to one with low risk of thromboembolic events or other treatment side effects. Administration via port infusion was associated with a negative willingness-to-pay amount, indicating that participants were not willing to pay for a treatment administered via port infusion versus intravenous infusion.

As with any survey, self-reporting bias is a limitation of our study. Also, because participants were enrolled from only two centres in one country, the generalizability of the findings is limited.

In summary, the findings of this DCE demonstrate that PwHA and caregivers most value treatments that offer improved QoL (e.g., maximizing the ability of PwHA to perform normal activities without bodily pain or fear of bleeding) and less invasive administration (subcutaneous over intravenous) have a low risk of thromboembolic events or other side effects and can be used both to prevent and treat emergency bleeds. PwHA and caregivers are also significantly influenced by annual bleeding rate, likelihood of inhibitor development and frequency of treatment administration. Most of these attributes are more associated with non-factor therapies, such as emicizumab, than with factor therapies. Such preferences may be important in maximizing treatment adherence. These findings are in line with those of similar previous studies.^{8–10} By including additional options for frequency and method of administration in this study, further insights into attributes of non-factor treatments are provided.

Out-of-pocket cost was a significant influencing factor but did not dominate preferences. Willingness-to-pay values from this analysis could be used as a basis for determining cost-effectiveness thresholds in future economic assessments of haemophilia A treatments.

KEYWORDS

discrete choice experiment, factor VIII prophylaxis, haemophilia A, non-factor therapy, treatment preference

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RKJ has been a consultant for and has received research funding from Genentech. KR and AP are employees of Genentech and hold stock. MSB, DH, LS and AM have no conflicts of interest to declare. Payment was received by Tulane University and funded by Genentech, Inc. to perform research.

AUTHOR CONTRIBUTIONS

All authors contributed to the conception and design of the study and to interpretation of the results. MB conducted patient recruitment, data collection and regulatory oversight and compliance. AM managed patient data entered on REDCap, patient follow-up for data and contributed to regulatory oversight. AP, KR and LS contributed to protocol development. RKJ and colleagues managed the study at the Seattle site. DH conducted the statistical analysis. All authors contributed to the drafting of the paper or to revising it critically for intellectual content. All authors gave final approval of the version to be published and agree to be accountable for all aspects of the work.

DATA AVAILABILITY STATEMENT

The data that support the findings of this study are not publicly available due to privacy and ethical restrictions.


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