Impact of severe haemophilia A on patients’ health status: results from the guardian™ 1 clinical trial of turoctocog alfa (NovoEight®)

M. OZELO,* P. CHOWDARY,† A. REGNAULT‡ and A. K. BUSK§

*IHTC “Claudio L. P. Correa”, INCT do Sangue Hemocentro UNICAMP, University of Campinas, Sao Paulo, Brazil; †Katharine Dormandy Haemophilia Centre and Thrombosis Unit, Royal Free London NHS Foundation Trust, London, UK; ‡Mapi, Lyon, France; and §Novo Nordisk A/S, Soeborg, Denmark

Summary. Haemophilia and its treatment interfere with patients’ life and may affect adherence to treatment. This study explored the impact of severe haemophilia A on patients’ health status, especially in young adults (YA), using data from guardian™ 1, a multinational, open-label, non-controlled phase 3 trial investigating safety and efficacy of turoctocog alfa (NovoEight®) in previously treated patients aged 12 years and older with severe haemophilia A (FVIII ≤ 1%). Health status was assessed using the EuroQoL-5 dimensions (EQ-5D-3L), covering 5 dimensions of health (mobility, self-care, usual activities, pain/discomfort and anxiety/depression), and a visual analogue scale (VAS) measuring self-rated overall health status. EQ-5D was administered pretreatment (screening/baseline) and posttreatment (end-of-trial). Baseline responses to the EQ-5D dimensions and VAS were described overall and by age and compared to reference values from UK general population. Guardian™ 1 included 150 patients (16 adolescents, 83 YA aged 16–29 and 51 adults aged 30+). All five dimensions of patients’ health status were impacted at baseline. The percentage of haemophilia patients reporting problems was consistently significantly greater than age-matched general population reference values. Likewise, for all age groups mean baseline EQ-5D VAS score was significantly lower for haemophilia patients (YA: 78.0) than for the general population (YA aged 18–29: 87.3). The health status of patients with severe haemophilia A entering guardian™ 1 was markedly poorer than that of the general population, particularly regarding mobility and pain. YA patients reported better health status than older patients, but considerably lower than that of the general YA population.

Keywords: haemophilia, health status, prophylaxis, questionnaires, turoctocog alfa

Introduction

Haemophilia A is an X-linked hereditary bleeding disorder resulting from lack or deficiency of clotting factor VIII (FVIII), causing excessive bleeding and easy bruising. Bleeding episodes are primarily treated by replacement of the missing clotting factor with recombinant or plasma derived FVIII concentrate, either as they manifest or preventively (as a prophylaxis regimen). Since the introduction of factor replacement therapy, life expectancy and quality of life of haemophilia patients have greatly improved [1,2]. However, treatment-related complications –including development of inhibitors to FVIII, venous access problems, infusion-related pain and interference with lifestyle associated with the time-consuming nature of the treatment – impact patients’ lives and may affect adherence to treatment [3].

Despite continuing efforts to better understand the experience of patients with haemophilia [4–6], data regarding their health-related quality of life (HRQoL) and health status are still limited. Adolescence and early adulthood are critical transitional periods for patients with chronic diseases [7,8], especially haemophilia [9,10]. This period is a time of physical, psychological and social developmental changes, which naturally impact patients’ attitudes towards their condition and its management. In addition, the functional deficits related to haemophilia may be particularly detrimental at an age when physical activity is of prime importance. Therefore, any opportunity to better understand the impact of haemophilia on patients, especially adolescents and young adults (YA), is valuable.
The objective of our analyses was to gain better insight into the impact of haemophilia on patients’ health status, in particular YA, using EuroQol-5 Dimensions–3 Levels (EQ-5D-3L) data collected in guardian™ 1, a phase III trial conducted to investigate safety and efficacy of turoctocog alfa (NovoEight®). This new recombinant FVIII compound, in adolescent and adult patients with severe haemophilia A. The generic assessment of health status EQ-5D-3L was used in the trial to complement the findings of the haemophilia-specific HRQoL instruments (HAEMO-QOL and HEM-A-QOL) [11]. In particular, the EQ-5D-3L allows generating patient-reported outcomes data that can be compared across various populations. The first aim of these analyses was to characterize the health status of these patients and compare it with that from a sample of the general population, explore the relationship (if any) between health status and national economic wealth and investigate change in health status over the course of the trial. Secondly, we set out to explore how haemophilia A patients perceive their own health status in comparison with the societal perception of their health.

Materials and methods

Study design and patient population

This study used data from the phase III multinational, open-label, non-controlled guardian™ (Novo Nordisk) 1 trial investigating safety and efficacy of prophylactic treatment with turoctocog alfa. Further details on study design and on the safety and clinical efficacy results of guardian™ 1 are reported elsewhere [12].

In accordance with the study protocol, enrolled patients had a documented history of at least 150 exposure days (EDs) to FVIII products (with a median of 516 EDs) and a negative history of FVIII inhibitors, no increased risk of thromboembolic events and, if HIV positive, a CD4+ lymphocyte count above 200 µL⁻¹. Patients received prophylactic turoctocog alfa replacement therapy dosed at either 20–40 IU kg⁻¹ every second day or 20–50 IU kg⁻¹ three times weekly, for between 75 and 85 EDs. The trial was conducted in the following countries: Brazil, Croatia, Germany, Israel, Italy, Japan, Malaysia, Russian Federation, Serbia, Spain, Switzerland, Taiwan, Turkey, UK and USA.

Guardian™ 1 was approved by all relevant independent ethics committees and institutional review boards. All patients or their legally authorized representatives provided written informed consent before any trial-related activities. The trial was conducted in accordance with the Declaration of Helsinki and Good Clinical Practice and was registered at www.clinicaltrials.gov (NCT00840086).

The EQ-5D-3L

Health status was a secondary endpoint in the trial and was assessed using the EQ-5D-3L instrument, a widely used generic patient-reported outcome measure. Patients completed the EQ-5D-3L when entering the trial (before starting treatment) and again at their end-of-treatment visit.

The EQ-5D-3L is a self-administered, generic, utility instrument developed by the EuroQol Group in 1990 [13]. It consists of five single-item dimensions: mobility, self-care, usual activities, pain/discomfort and anxiety/depression. For each dimension, the responder indicates his own state on a 3-level response scale ranging from ‘no problems’ to ‘severe problems’. A newer version of the EQ-5D with a 5-level response scale has since been developed [14] but was not available at the time of the trial, so the older 3-level version was used. The five EQ-5D-3L dimensions can be treated separately or in combination, where they constitute a health state. For economic analysis, each health state can be converted into a utility value, referred to as the EQ-5D index score, by applying a country-specific tariff (i.e. the value the general population places on each health state). In this analysis, the EQ-5D index scores were derived using the UK tariff based on the time trade-off methodology. The EQ-5D index score can only be calculated if responses to all five EQ-5D items are available.

In addition to the five items, the questionnaire contains a 10 cm vertical visual analogue scale (VAS) on which patients must rate (evaluate) their own current health states. The EQ-5D VAS ranges from 0 (worst imaginable health state) to 100 (best imaginable health state).

Statistical analysis

The EQ-5D items, EQ-5D VAS and EQ-5D index score observed at baseline in guardian™ 1 were compared with gender- and age-specific reference values (available from 18 years of age) from a UK general population sample [15]. The EQ-5D items were compared between groups using a chi-squared test, and mean EQ-5D VAS was compared between groups using a t-test. The EQ-5D items and VAS at baseline were also described for the subset of patients who were HIV-positive. The baseline values and changes from baseline to end-of-trial in EQ-5D VAS were described according to the treatment regimen received before the trial (prophylaxis, on-demand or mixed) in the full sample and for each age group (adolescents aged 12–15 years, YA aged 16–29 years and adults aged 30–60 years).
To explore the association between patients’ health status and the economic wealth of their respective countries, gross domestic product (GDP) per capita based on purchasing power parity (PPP) was used as a proxy for countries’ economic wealth. The GDP (PPP) per capita of 2011 for the 15 countries included in the trial was obtained from the International Monetary Fund’s World Economic Outlook (WEO) Database of April 2013 [16]. Mean baseline EQ-5D VAS scores for each country were plotted as a function of the GDP (PPP) per capita. Pearson correlation coefficients (r) were also calculated to investigate the relationship between mean EQ-5D VAS scores and GDP (PPP) per capita. Similarly, for each country and each EQ-5D dimension, the percentage of patients declaring any problems (whether moderate or extreme) at baseline was plotted as a function of GDP (PPP) per capita of the country.

To explore the relationship between patients’ own evaluations of their health status (measured by the EQ-5D VAS) and the corresponding societal perception of patients’ health (measured by EQ-5D index score), Pearson correlation coefficients were calculated between the EQ-5D VAS and the EQ-5D index scores. All data processing and analyses were performed using SAS software for Windows v9.2 (SAS Institute, Inc., Cary, NC, USA).

## Results

### Study population

A total of 150 patients with severe haemophilia A were enrolled in guardian™ 1:16 adolescents (aged less than 16), 83 YA (aged 16–29) and 51 adults (aged 30 or older) (Table 1). The median age in these three groups was 13.5, 22.1 and 41.8 years, respectively. Before entering the trial, 33% of patients in the full sample had received a prophylaxis regimen, 39% a non-prophylaxis (on-demand) regimen and 27% a mixture of the two. A smaller share of YA (33%) than adolescents (44%) and adults (47%) had received on-demand treatment before the trial. Fourteen patients included in the trial were identified as HIV-positive patients: 12 HIV antibody positive patients and 2 HIV antibody inconclusive patients that were identified as HIV positive based on other measurements. Most of them were older than 30 (n = 12).

### Table 1. Baseline demographics and clinical characteristics of patients included in guardian™ 1 for full sample and by age groups.

| Age, years | Adolescents (12–15 years) | Young adults (16–29 years) | Adults (≥30 years) | Full sample |
|------------|---------------------------|---------------------------|-------------------|-------------|
| Mean (SD)  | 13.5 (1.0)                | 22.1 (3.9)                | 41.8 (8.5)        | 27.9 (11.8) |
| Median     | 13.5                      | 22.0                      | 41.0              | 25.0        |
| Min–Max   | 12–15                     | 16–29                     | 30–60             | 12–60       |
| BMI, kg/m²| 18.6 (2.6)                | 24.0 (4.5)                | 26.0 (4.7)        | 24.1 (4.9)  |
| Time since diagnosis of haemophilia A, years | Mean (SD) | 12.1 (2.8) | 21.4 (4.7) | 39.1 (8.9) | 26.3 (11.4) |
| Median     | 13.0                      | 21.0                      | 38.0              | 24.0        |
| Min–Max   | 5–15                      | 8–29                      | 19–59             | 5–59        |
| Type of management before the trial, n (%) | Prophylaxis | 3 (18.8) | 30 (36.1) | 17 (33.3) | 50 (33.3) |
|           | On-demand                 | 7 (43.8)                  | 27 (32.5)         | 24 (47.1)  | 58 (38.7)  |
|           | Mixed regimen             | 6 (37.5)                  | 25 (30.1)         | 10 (19.6)  | 41 (27.3)  |

### Analysis of baseline self-reported health status of patients in guardian™ 1

The percentage of patients in guardian™ 1 who reported problems at baseline increased with age for all EQ-5D dimensions, except anxiety/depression problems, which were reported by a larger percentage of adolescents than YA (Table 2). Overall, self-rated health status as assessed by the EQ-5D VAS also worsened with age.

The percentage of people reporting problems was significantly higher for patients with haemophilia than in the reference population (P ≤ 0.001 for all EQ-5D items). The most remarkable differences between patients with haemophilia and the reference population were observed in the mobility and pain/discomfort domains for both YA and older adults. Of the YA with haemophilia, 41% reported mobility problems, compared with only 5% of the general YA male population (aged 18–29 years). Similarly, 59% of YA with haemophilia reported problems with pain/discomfort, compared with only 16% of YA in the general population sample.

The overall self-rated health status as assessed by the EQ-5D VAS was significantly poorer (P < 0.001) for haemophilia patients than the reference population, both for YA (78.0 vs. 87.3) and adults (66.2 vs. 85.2).

HIV-positive patients indicated fairly similar health status as the group of adult patients aged 30 or older as a whole, although a greater proportion (92.9% vs. 76.5%) reported pain/discomfort problems. On the other hand, the proportion of these patients who reported anxiety/depression problems was lower (28.6% vs. 41.2%). The mean overall self-rated health status assessed by the EQ-5D VAS was slightly lower for HIV positive patients than that for the entire group of adult patients aged 30 or older (59.8 vs. 66.2).

The correlation between the mean EQ-5D VAS at baseline for each country represented in guardian™ 1 and its GDP per capita was null, indicating the absence of an association between health status reported by patients with haemophilia and their respective countries’ economic wealth (Fig. 1). The correlation between the percentage of patients reporting problems in each of the five EQ-5D items in each country, and the GDP per capita was at best moderate (r = −0.428 for self-care) (data not shown).
Table 2. Description of EQ-5D items and VAS at baseline in adolescents, young adults and adults aged 30–60 years in guardian™1 (n = 150), and UK reference values [15].

| EQ-5D item/score                  | Adolescents                                      | Young adults                                    | Adults 30–60 years                               |
|----------------------------------|--------------------------------------------------|------------------------------------------------|------------------------------------------------|
|                                  | guardian™1 (12–15 years, n = 30)                  | guardian™1 (16–29 years, n = 83)                 | guardian™1 (30–60 years, n = 753)               |
| Mobility problems, n (%)         | 4 (25.0)                                          | 13 (25.5)                                       | 29 (26.6)                                      |
| Self-care problems, n (%)        | 2 (12.5)                                          | 3 (1.0)                                         | 200 (26.6)                                     |
| Usual activities problems, n (%) | 6 (37.5)                                          | 47 (16.4)                                       | 76.0 (18.1)                                     |
| Pain/Discomfort problems, n (%)  | 5 (31.3)                                          | 30 (10.4)                                       | 67.3 (13.9)                                    |
| Anxiety/Depression problems, n (%)| 88.4 (10.8)                                      | 138 (18.3)                                      | 85.2 (37.2)                                    |
| EQ-5D VAS, mean (SD)             | 84.4 (10.8)                                      | 87.3 (13.9)                                    | 85.2 (37.2)                                    |
| UK reference values              |                                                  |                                                 |                                                |


description of change in self-rated health status during the trial according to previous treatment regimen

Overall, the baseline self-rated health status (EQ-5D VAS) was comparable regardless of the treatment regimen patients had received prior to the trial (Table 3). In the full sample, the change in EQ-5D VAS over the course of the trial was marginal for patients who were previously treated with either prophylaxis or on-demand therapy, whereas there was a notable improvement for patients who had received a mixture of the two regimens. For adults aged 30 years or older, the change from baseline in EQ-5D VAS did not clearly differ according to the treatment regimen received before the trial. In the YA group, however, the mean change in EQ-5D VAS showed a notable improvement for patients who were previously treated on-demand (5.2-point improvement) or with a mixed-treatment regimen (8.6-point improvement), while it remained similar for patients who were already on prophylaxis before the trial. As the adolescent sample size was small, the subgroup analysis according to the previous treatment regimen involved even smaller samples still, thus preventing a meaningful interpretation of the results.

Association between EQ-5D VAS and EQ-5D index score

The EQ-5D VAS and EQ-5D index score were moderately correlated (r = 0.52) in the overall full sample and for YA (r = 0.55). Neither the EQ-5D VAS nor the index score were consistently greater than one another (Fig. 2).

Discussion

The objective of this study was to investigate the health status of patients with severe haemophilia A aged 12–60 years, using EQ-5D-3L data collected in a phase III multinational clinical trial, guardian™1 [12]. Patients with haemophilia A included in guardian™1 clearly showed poorer health status than the general population and more frequently reporting problems in all five dimensions of the EQ-5D-3L, as well as in self-rated overall health status (EQ-5D VAS). This finding emphasizes the human impact of haemophilia, which was shown to be particularly remarkable in YA patients.

Regardless of age, the most salient problems reported by patients in guardian™1 were mobility issues and pain. These findings are in line with the few previously published data on health status of haemophilia patients, which also showed that these patients have a markedly poorer health status than the general population, particularly in terms of mobility and pain [5,17–20]. Hence, these dimensions should be considered carefully in the management of patients with haemophilia A. In guardian™1, HIV-positive patients did not have a substantially worse health status than other adult patients, although they did report a slightly worse self-reported overall health status. Pain problems tended to be more frequent and anxiety/depression problems less frequent in HIV-positive patients. Nonetheless, these findings should be considered cautiously, given the small number of patients involved.

In guardian™1, improvements in self-rated health status of patients treated with turoctocog alfa, as assessed by the EQ-5D-3L, were only observed for patients who were switched from mixed treatment regimen to prophylaxis as a consequence of entering the trial. In YA, however, the improvement in health status was observed both among patients who were previously treated with non-prophylaxis only and among those who were previously treated with a mixed regimen, suggesting a benefit of prophylaxis therapy for YA with haemophilia A [11,21].

In terms of the relationship between health status and national wealth, it could reasonably be assumed that poorer countries would have more health problems than richer ones. This was also indicated in the international study in which the EQ-5D-3L reference values were generated; a negative correlation was observed between self-reported health problems and GDP per capita, and there was a strong (r = 0.65) positive relationship between patients’ health status as assessed by the EQ-5D VAS and GDP per capita.
These associations were not found in guardian™ 1; the correlation of the EQ-5D VAS score and the percentage of patients reporting health problems with GDP per capita was very weak. It should be noted that these cross-national comparisons could be impacted by cross-cultural differences in how patients report their experiences [22]. Furthermore, this may also be linked to access to FVIII in different countries. In this respect, we tried to explore the association between health status, as measured by the EQ-5D, and FVIII consumption at the country level, using the information from the report of the World Federation of Haemophilia (WFH) 2012 annual survey [23] and no clear association was found. However, this analysis was not fully satisfactory: it did not take into account the many factors that can interfere in the association, and the data available on the FVIII consumption are probably questionable (the information was missing for 6 of the 16 countries of the trial and the WFH report acknowledges that the available data on FVIII consumption should be used cautiously). Hence, as this analysis and its conclusions were uncertain, we preferred not reporting it here. A more thorough research, specifically devoted to this question would probably be needed to accurately inform the association between patients’ health status and the management of patients with haemophilia at the societal level.

The EQ-5D index score reflects societal preferences for health status, while the EQ-5D VAS reflects the respondent’s individual valuation of their own health status. Hence, to a certain extent, comparing these two measures reveals the difference between the individual and the societal valuation of a given condition. In guardian™ 1, the correlation between these two assessments was moderate (slightly greater than 0.5), indicating that the perspectives of society and of the patients themselves on their health status were fairly well aligned. An interesting follow-up question would be whether patients systematically judge their health status as being better (or worse) than society does. In this regard, data from the guardian™ 1 trial do not clearly indicate over- or under-estimation of the health status of patients by society.

This study presented here does have some limitations. Our analyses used data from a phase III clinical trial that was not specifically designed to characterize the impact of haemophilia on patients’ health status. For example, the patient sample was selected according to strict inclusion and exclusion criteria aligned with the primary objective of the trial, and was not intended to be representative of the general population of patients with severe haemophilia A. In addition, even though guardian™ 1 was a reasonably large haemophilia trial, the sample size was still relatively small. Thus, any generalization of our findings should be treated with caution. Finally, the nature of EQ-5D data introduces some caveats to the interpretation of these analyses. Firstly, the EQ-5D-3L is a generic
instrument that may not capture specific aspects of patients’ health statuses, especially since the 3-level (rather than 5-level) version of the instrument was used for this study. For example, mobility was identified as a problematic dimension for patients with haemophilia. However, none of the patients used the most extreme mobility response option (‘confined to bed’); thus, in practice only two levels of mobility were recorded (‘no problems in walking about’ and ‘some problems in walking about’). A finer distinction of the mobility problems encountered by patients may have allowed their impact to have been characterized more precisely. In addition, the computation of the EQ-5D index score and the comparison to population norms demanded ‘localization’ (i.e. required the choice of a set of local references). For simplicity and consistency reasons, these analyses were performed using UK values. These values were selected because the EQ-5D-3L was originally developed in the UK, and the UK values are undoubtedly the most widely used. However, this does mean that our analyses were, in part, subject to a UK perspective. It would be interesting to explore whether this selection of values had an effect on our findings. Another limitation was that EQ-5D-3L data were collected from individuals under 18 years of age, for whom no reference data exist, thus preventing proper characterization of the impact of haemophilia on adolescents’ health status.

The relationship between the health status of patients with haemophilia and their treatment could be explored further, perhaps by considering the long-term impact of prophylaxis. The relationship between health status and clinical outcomes would also be a relevant research area; for example, the link between health status and annual bleeding rates or measures of joint bleeds/pathology could be explored.

Table 4. Mean EQ-5D VAS at baseline and change from baseline to end-of-trial visit according to the treatment received before the trial in guardian™ 1 for full sample and by age group.

| Previous treatment | Prophylaxis | Non-prophylaxis | Mixed |
|-------------------|-------------|-----------------|-------|
|                   | Baseline EQ-5D VAS | Change in EQ-5D VAS | Baseline EQ-5D VAS | Change in EQ-5D VAS | Baseline EQ-5D VAS | Change in EQ-5D VAS |
| Full sample       | n = 47       | 75.2 (16.3)     | 0.4 (16.7) | 53 | 75.7 (18.0) | 0.9 (14.4) | 39 | 73.4 (22.9) | 7.0 (16.0) |
| Adolescents 12–15 years | n = 2       | 89.0 (1.41)    | -4.5 (19.1) | 7 | 89.7 (7.4)   | -6.0 (18.6) | 6 | 86.7 (15.9) | 6.4 (12.1) |
| Young adults 16–29 years | n = 28      | 78.0 (17.2)    | 1.2 (18.5) | 24 | 79.4 (16.3) | 5.2 (10.34) | 23 | 76.2 (21.5) | 8.6 (18.8) |
| Adults 30–60 years | n = 17      | 68.9 (13.6)    | -0.3 (14.2) | 22 | 67.2 (18.3) | -1.5 (15.7) | 10 | 59.2 (24.1) | 3.9 (10.7) |

Fig. 2. Scatter plot of EQ-5D VAS and EQ-5D index score according to age groups.

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In conclusion, our analysis demonstrated that the health status of patients with severe haemophilia A included in guardian™ 1 was markedly poorer than that of the general population, particularly regarding mobility and pain. Although YA patients reported better health status than older patients, their health status was still considerably lower than that of the general YA population. Finally, the main driver for improvement in health status of haemophilia A patients was the switch from mixed regimen therapy to prophylaxis, which was shown to be particularly beneficial in the YA group.

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Authors’ contributions

MO, PC and AKB made substantial contributions to analysis and interpretation of data. AR designed and performed data analyses and participated in data interpretation. All authors assisted with the manuscript outline, gave input, reviewed and approved the manuscript.

Disclosures

MO has received research support from Bayer, Baycr, Biogen, CSL Behring and Novo Nordisk and has been a paid speaker for Bayer and Novo Nordisk. PC has received travel grants and served on advisory boards for Bayer, Baxter Healthcare, Biogen Idec, CSL Behring, Novo Nordisk, and Pfizer; and has received research funding from CSL Behring, Novo Nordisk, and Pfizer. AKB is an employee of Novo Nordisk A/S. AR, an employee of Mapi, was a paid consultant to Novo Nordisk A/S.

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