

Quality of Life Related to Oral versus Subcutaneous Iron Chelation: A Time Trade-off Study

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ABSTRACT

Objective: To investigate the utility associated with subcutaneous infusion (deferoxamine) compared with once-daily oral administration (deferasirox) of iron chelation therapy.

Methods: Interviews using the time trade-off technique were used to estimate preferences (utility) for health states by finding the point at which respondents were indifferent between a longer but lower quality of life (QoL) and a shorter time in full health. Participants (n = 110) were community-based, 51% women, median age 35 years, from four regions in Sydney, Australia. Respondents rated three health states involving equal outcomes for people with thalassemia but with different treatment modalities for iron chelation; an “anchor state” describing a patient receiving iron chelation without administration mode specified, anchor state plus iron chelation via subcutaneous infusion, and anchor state plus iron chelation through once-daily oral medication.

Results: On an interval scale between 0 (death) and 1 (full health), median (interquartile range) utility of 0.80 (0.65–

0.95) for the anchor state, 0.66 (0.45–0.87) for subcutaneous infusion, and 0.93 (0.80–0.97) for once-daily oral administration was obtained. The mean (median) difference of 0.23 (0.27) between the two treatments was statistically significant (Wilcoxon-signed rank test, $P < 0.001$). Subcutaneous infusion was associated with a mean (median) utility 0.13 (0.14) lower than the anchor state ($P < 0.001$), and once-daily oral treatment had a utility 0.10 (0.13) higher ($P < 0.001$).

Conclusion: Community respondents associate oral administration of an iron chelator such as deferasirox with enhanced QoL compared with subcutaneous treatment. Assuming equal safety and efficacy, QoL gains from once-daily oral treatment compared with subcutaneous infusion are significant.

Keywords: administration route, iron chelation, quality of life, time trade-off.

Introduction

The health-related quality of life (HRQoL) of patients has become increasingly important when considering options for individual patient care and in allocating health-care resources between competing treatments. Chronic iron overload is a major complication of potentially lifesaving blood transfusions used in the ongoing treatment of hematological conditions such as the thalassemias, myelodysplastic syndrome, and sickle cell disease. Excess iron is deposited in various tissues of the body, particularly the liver, heart, and endocrine organs [1]. Once the body's storage capacity is exceeded, free iron catalyzes the formation of highly

reactive hydroxyl radicals which lead to membrane damage and denaturation of proteins. This process leads to tissue damage and ultimately to significant morbidity and mortality.

The current standard of care for chronic iron overload is the subcutaneous administration of deferoxamine, for 8 to 12 hours per day, 5 to 7 days a week. This treatment regimen in some cases leads not only to poor compliance, and hence a reduction in the extent of effective iron chelation, but also to a reduction in HRQoL.

Deferasirox, a recently developed treatment for transfusional iron overload, is a once-daily oral therapy [2,3]. Evidence to date indicates that this treatment has equivalent efficacy to subcutaneous deferoxamine [2]; however, little is known about the comparative HRQoL impacts of these alternative treatments. There has been a dearth of research exploring the HRQoL impacts of iron overload treatments

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including the route of administration, although a preliminary study using the Sickness Impact Profile indicated that route of administration affected patient-perceived HRQoL [4].

The current study aimed to elicit the strength of community preferences (utility) between the different modes of administration where the current standard treatment, deferoxamine (subcutaneous administration), was compared with the new once-daily oral treatment, deferasirox.

Methods

A community sample of 120 individuals was asked to participate in a time trade-off (TTO) exercise. The participants of the study were registrants of a market research firm and were systematically sampled from four geographic regions across Sydney, Australia. These regions represented a range of sociodemographic characteristics, and a balanced sample across socioeconomic status, age, and sex was recruited. Respondents received a fee of AUS\$45 at the end of each interview. Ethics approval for the study was not required as the registrants were not patients, no interventions were involved, and they had previously consented to occasional surveys.

At interview, each participant was presented with standardized background information on iron overload and its treatment, together with short descriptions (vignettes or scenarios) of three health states for patients with thalassemia. These vignettes were designed to be clinically and domestically realistic, and easily understood. Each of the vignettes is presented in Box 1, and can be summarized as follows: 1) an anchor/base state that described a patient who has iron chelation without describing the treatment itself; 2) the anchor state plus iron chelation via a subcutaneous infusion; and 3) the anchor state plus iron chelation via a once-daily oral medication.

An iterative approach was used to develop the vignettes. That is, draft vignettes were shown to hematology clinical specialists and people currently treated for thalassemia to ensure that the descriptions were clinically accurate, reflected the experiences of the target patient population, and accurately represented the necessary dimensions of HRQoL. Consultation on the content of those vignettes continued until consensus was achieved between the researchers, clinicians, and people with thalassemia.

Following standard TTO methodology [5,6], participants were then asked systematically to make a series of hypothetical trade-offs between living in each of these health states for 10 years, or shorter periods in "normal health." At the point of indifference, where the participant was unable to choose between 10 years in the alternative health state and the period of normal

health on offer, the participant implicitly assigned equivalent value to the alternatives offered. The "quality" weight then assigned, known as the level of "utility" in economic evaluation, is the ratio of the time in normal health on offer to the time in the alternative health state (10 years).

To avoid ordering bias, respondents were randomized to respond to either health state (2) or (3) immediately after their response to the anchor state. These health states were not labeled in terms of the iron chelator included and differed only in their description of the mode of treatment administration. The range of possible utility values was a maximum of 1 for full health and a minimum of 0 for death.

Five novice interviewers received a training for two full days by an experienced "master" interviewer. This involved theoretical background, up to eight training interviews with administrative staff, observation of at least 16 interviews and accompanying commentary by the trainer. These initial 16 interviews were undertaken with one interviewer observing. During the study, quality control interviewer meetings were held after every 20 to 25 interviews. Given that the TTO exercise can be difficult for some interviewees and limited relevant data were available to assist with sample size estimation, 16 initial interviews were conducted. Investigators and interviewers reviewed each initial case to identify potential difficulties participants were having with understanding the TTO technique, whether interviewers were consistent with their oral presentation of vignettes and how they reached the point of indifference, and that the content of the vignettes was acceptable to participants. No anomalies were revealed, so no changes were made to the vignettes or procedures.

Based on the first 16 interviews, the standard deviation across the three vignettes ranged from 0.29 to 0.35. We then estimated that at least 100 complete interviews would give sufficient power to detect a difference in mean utility scores of 0.1 where $\alpha = 0.05$, power = 80%. A 10% difference in mean utility score was chosen because it was considered that this represented an important difference in QoL [7]. As the primary objective of this study was to compare individual respondents' scores across the two routes of administration, the nonparametric Wilcoxon-signed rank test was used. With TTO, as some respondents may have extreme points of view and/or will not trade, this conservative nonparametric procedure was preferred over the parametric paired *t*-test equivalent. Differences in utility values between demographic factors were explored with the Mann-Whitney *U*-test (two groups) or Kruskal-Wallis test (two or more groups). The possible effects of vignette ordering bias were examined using the Mann-Whitney *U*-test. All analyses were undertaken using SPSS version 14 (SPSS Inc., Chicago, IL, USA).

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