A Time-Cost Augmented Economic Evaluation of Oral Deferasirox versus Infusional Deferoxamine for Patients with Iron Overload in South Korea

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ABSTRACT

Objectives: This study aims to conduct an economic evaluation of oral deferasirox (DSX) compared with infusional deferoxamine (DFO) in patients with transfusional iron overload.

Methods: Depending on the methods for measuring time-cost and convenience associated with the mode of administration, either cost-utility analysis or cost-effectiveness analysis was undertaken. The difference in compliance rate between DSX and DFO was applied.

Results: Although the drug cost of DSX was US$124,070 higher than that of DFO (US$96,039 vs. US$220,199), all other costs were lower in patients with DSX than in patients with DFO. In the cost-utility analysis, DSX resulted in US$3197 savings with a gain of 2.63 quality-adjusted life-years per patient. The result of the cost-effectiveness analysis also showed that DSX dominated DFO.

Conclusions: With a considerable improvement in convenience and injection time rather than efficacy, DSX is considered as a dominant therapy for patients with iron overload.

Keywords: compliance, cost-effectiveness analysis, cost-utility analysis, iron chelating agents.

Introduction

The majority of patients with β-thalassaemia, sickle cell disease (SCD), myelodysplastic syndromes (MDS), and other types of anemia often experience iron overload because of repeated transfusions. Iron overload increases the iron burden of the body, resulting in impairment of the heart, liver and endocrine function, and death [1]. Because humans have no physiological mechanisms to eliminate iron from their bodies, iron chelation therapy (ICT) has been recommended for transfusion-dependent patients with iron overload. Infusional deferoxamine (DFO) is known to be efficacious as a chelating agent [2,3]. Nevertheless, because of its very poor oral bioavailability and its short half-life, DFO must be administered in a continuous infusion for 8 to 12 hours, 5 to 7 days a week. Regular infusions are painful and cumbersome; thus, its effectiveness has been limited mainly by poor compliance.

Although infusion of DFO using a portable pump at home is allowed in European countries and the United States, DFO can be administered via slow subcutaneous or intravenous infusion only in hospitals in South Korea. Thus, the medical and time costs of infusion for DFO may be higher and the compliance is likely to be lower in South Korea than in other countries (for details, see A Time-cost Augmented Economic Evaluation of Oral Deferasirox versus Infusional Dereroxmine for Patients with Iron Overload in South Korea Value in Health Supporting Information, Part I at: http://www.isPOR.org/Publications/value/ ViHsupplementary/ViH12s3_Kim.asp).

Deferasirox (DSX) was recently licensed as an oral ICT in South Korea. DSX phase II/III clinical trials have shown that efficacy of DSX is similar to that of DFO [4–9]. In addition, DSX is expected to have more convenience and lower administration time [4,10].

This study aims to conduct an economic evaluation of DSX compared with DFO in transfusion-dependent patients, focusing especially on the main differences in medication time and convenience between oral and infusion therapy associated with the mode of administration.

Methods

Clinical Trials

A comparative phase III clinical trial in regularly-transfused patients with β-thalassaemia was conducted to demonstrate the efficacy of DSX versus DFO [4–6,8]. The clinical trial showed noninferiority of 20–30 mg/kg/day for DSX versus equivalent doses for DFO in patients with a baseline LIC of ≥7 mg Fe/g dw (for details, see A Time-cost Augmented Economic Evaluation of Oral Deferasirox versus Infusional Dereroxmine for Patients with Iron Overload in South Korea Value in Health Supporting Information, Part II at: http://www.isPOR.org/Publications/value/ ViHsupplementary/ViH12s3_Kim.asp). Phase II clinical trials in patients with SCD, MDS, and other rare types of anemia have shown similar results in Phase III clinical trials in patients with β-thalassaemia [7,9].

Patient Population

In this study, the patients were transfusion-dependent patients requiring ICT because of iron overload. The patients with β-thalassaemia, SCD, MDS, and other rare types of anemia were included. The standard patient was assumed to weigh 50 kg and this patient started chelation therapy at 50 years old (for details, see A Time-cost Augmented Economic Evaluation of Oral Deferasirox versus Infusional Dereroxmine for Patients with Iron Overload in South Korea Value in Health Supporting Information, Part III at: http://www.isPOR.org/Publications/value/ ViHsupplementary/ViH12s3_Kim.asp).

Model Overview

DFO must be infused over 8–12 hours per day for 5–7 days a week, while DSX is a once-daily oral chelation agent. There may
be significant differences between DFO and DSX in terms of convenience and time-saving. There is no guideline regarding whether the outcome should be life-years gained (LYG) or quality-adjusted life-years (QALYs) when differences in convenience and time-saving are evaluated. Thus, depending on the method measuring this convenience associated with the mode of administration, either a cost-utility analysis or a cost-effectiveness analysis was undertaken. In addition, the results of these analyses were compared.

In the cost-effectiveness analysis, the administration and travel time cost were calculated as indirect costs and the outcome was presented in terms of LYG. When the convenience due to the use of DSX compared with DFO was considered as a utility, a cost-utility analysis was conducted. Indirect costs—productivity loss due to the injections and visits to the hospital—were excluded in the lists of costs in the cost-utility analysis to avoid double counting.

A Markov model was used to estimate the incremental cost-utility ratio (ICUR) and the incremental cost-effectiveness ratio (ICER) of DSX versus DFO. The Markov health states were survival with ICT, survival without ICT, and death (see Fig. S1 at A Time-cost Augmented Economic Evaluation of Oral Deferasirox versus Infusional Dereroxmine for Patients with Iron Overload in South Korea Value in Health Supporting Information at: http://www.ispor.org/Publications/value/ViH12s3_Kim.asp). Although natural death depended on age, disease-specific death was allowed to vary with the compliance of ICT.

Future costs and QALYs were evaluated over a 50-year time-frame and discounted to their present value using an annual discount rate of 5%. A societal perspective was adopted.

Health Outcome and Compliance in an Economic Evaluation

The health outcomes of this study were LYG in a cost-effectiveness analysis and QALYs in a cost-utility analysis. The impact on survival of ICT was reported to depend on the compliance rate of ICT patients [2,11,12]. The study examined patients initiating ICT at 5 years old showed that life expectancy was 12.5 years with compliance under 75 times, 28.4 years with compliance between 75 and 225 times, 47.3 years with compliance between 225 and 300 times, and 57 years with compliance over 300 times per year [2,13]. Using this data, the continuous relationship with the mortality rate and the compliance rate was derived (for details, see A Time-cost Augmented Economic Evaluation of Oral Deferasirox versus Infusional Dereroxmine for Patients with Iron Overload in South Korea Value in Health Supporting Information, Part IV at: http://www.ispor.org/Publications/value/ViH12s3_Kim.asp). The compliance for oral deferiprone was reported to be 16% higher than that of DFO in clinical trials [14]. There was no clinical data regarding compliance of DFO in South Korea. Thus, compliance with DFO and DSX was assumed to be 64%, the reported average compliance rate and 74.24%, the estimated compliance rate of deferiprone, respectively, in the base case analysis of this study. To explore the impact of compliance with DFO on the results, a sensitivity analysis was performed.

The ICT patient-reported outcome showed DSX had a much higher score than DFO in terms of convenience, satisfaction, and preference [4,10]. Patients' quality of life was improved with oral ICT [15]. The utility outcomes associated with the mode of administration based on a community survey using the time trade-off method were employed. In this survey, mean utility weights of 0.75 (95% CI: 0.70–0.80) for the anchor state, which was considered as the utility weights of the patients who were not treated with ICT, 0.61 (95% CI: 0.55–0.67) for DFO, and 0.85 (95% CI: 0.81–0.89) for DSX were reported [16]. Clinical trials of DSX compared with DFO reported symptoms of side effects with two ICTs were temporary and negligible and did not affect patients’ quality of life [5,6]. Thus, this study did not consider these side effects.

Costs

When convenience and time-saving were considered as indirect costs, the list of costs included productivity loss associated with medical utilization. Drug treatment, physician fees, medical devices, and travel costs were included as the direct costs of DFO. In the list of the costs of oral DSX, medical devices for infusion and productivity loss due to injections were excluded.

Although common costs including the monitoring costs of the two drugs were excluded because of limited data, a creatinine clearance test cost was added to the list of DSX costs based on clinical trials in which DSX increased serum creatinine levels. Patients with DSX who received additional monitoring of creatinine levels were assumed to be able to control the creatinine levels and experience no advanced event because of the increased serum creatinine levels. Commonly occurring costs with different frequencies, such as physician fees and travel costs, were also considered in this study.

Table S1 (see Table S1 at A Time-cost Augmented Economic Evaluation of Oral Deferasirox versus Infusional Dereroxmine for Patients with Iron Overload in South Korea Value in Health Supporting Information at: http://www.ispor.org/Publications/value/ViH12s3_Kim.asp) shows the unit costs associated with DFO and DSX. The recommended doses of DFO and DSX depend on the level of transfusion, liver iron concentration, and on the weight of the patient. In this study, the daily dose for a patient weighing 50 kg was assumed to be 2000 mg for DFO and 1000 mg for DSX based on the directions of 40 mg/kg/day for DFO and 20 mg/kg/day for DSX [7]. The resource use of other medical costs of DFO was based on a hospital survey of ICT patients in South Korea.

The fee schedule of the Korean National Health Insurance in 2007 was used to calculate the drug costs, the physician fees, monitoring costs, and the material costs. Travel costs were established to be US$10.07 per round trip according to the National Health and Nutritional Examination Survey (for details, see Supporting Information, Part V at: http://www.ispor.org/Publications/value/ViH12s3_Kim.asp). The average wage rate of each age group in 2007 was calculated. Productivity loss due to utilization was estimated considering the labor participation rate and ages of the patients. Only half of the patients requiring ICT assumed to have an intention to work in this study.

Results

Base-Case Analysis

Although the discounted drug cost of DSX was US$124,070 higher than that of DFO (US$96,039 vs. US$220,199), all other costs including health service costs and time costs were lower in patients with DSX than in patients with DFO. These lower costs offset the higher drug cost of DSX. In the cost-utility analysis, DSX resulted in lower direct costs and higher QALYs gained (US$3197 savings with a gain of 2.63 QALYs per patient). The results of the cost-effectiveness analysis also showed that DSX dominated DFO in these measures (see Table S2 at A Time-cost Augmented Economic Evaluation of Oral Deferasirox versus
Infusions of Dereroxmine for Patients with Iron Overload in South Korea Value in Health Supporting Information at: http://www.ispor.org/Publications/value/ViHsupplementary/ViH12s3_Kim.asp).

Sensitivity Analysis

Given the compliance of DSX of 74.24%, for a sensitivity analysis, the compliance of DFO was varied from 1% to 74.24% (equivalent compliance of DSX). A decrease in the compliance of DFO indicates a relative increase in the compliance of DSX. The result of the sensitivity analysis showed that the relative improvement in the compliance rate for ICT leads not only to higher effects but also to higher costs, resulting in an increase in the ICUR or ICER (see Figs. S2–S5 at A Time-cost Augmented Economic Evaluation of Oral Deferasirox versus Infusional Dereroxmine for Patients with Iron Overload in South Korea Value in Health Supporting Information at: http://www.ispor.org/Publications/value/ViHsupplementary/ViH12s3_Kim.asp). After the difference between the compliance cost of the two drugs exceeded 58.24%, however, the ICUR decreased. The result of the sensitivity analysis of the cost-effectiveness analysis was similar. The relationship between the net cost and the net effect had a convex curve as the compliance rate of DFO decreased. When the difference in the compliance rate was 49.24% (25% for DFO, 74.24 for DSX), ICER was highest.

Trade-Off between QALY and Productivity Loss Costs

Let the incremental QOL (ΔQOL) be comprised of the incremental LYG (ΔLYG) and the incremental quality of life (ΔQOL). Because the incremental total costs (ΔTC) is sum of the incremental direct costs (ΔDC) and indirect costs (ΔIDC), ICUR

\[ \frac{\Delta DC}{\Delta QALY} \]

The absolute ratios of the incremental QOL to productivity loss \( \frac{\Delta IDC}{\Delta QOL} \). The absolute ratios of the incremental QOL to productivity loss were likely to be maintained at US$20,000, the implicit threshold of QALY in South Korea (see Fig. S6 at A Time-cost Augmented Economic Evaluation of Oral Deferasirox versus Infusional Dereroxmine for Patients with Iron Overload in South Korea Value in Health Supporting Information at: http://www.ispor.org/Publications/value/ViHsupplementary/ViH12s3_Kim.asp).

Discussion

Cost-utility analysis and cost-effectiveness analysis were conducted to present methods measuring convenience and time-saving associated with the mode of administration. Impact of an improvement in the compliance on the economic evaluation was also examined.

The results of the cost-utility analysis and cost-effectiveness analysis showed that a different conclusion could be derived. Nevertheless, knowing which is the more suitable model remains controversial.

The two base-case analyses showed that DSX saved on costs and gained effectiveness compared with DFO. When the gap between the compliance rates of the two ICTs exceeded 14.24% in the cost-utility analysis and 21.24% in the cost-effectiveness analysis, however, the costs of DSX became higher than those of DFO. Both ICUR and ICER increased until the compliance difference reached 58.24% (16% for DFO vs. 74.24% for DSX) in the cost-utility analysis and 49.24% (25% for DFO vs. 74.24% for DSX) in the cost-effectiveness analysis. This result showed that the relative improvement in compliance increased the treatment cost as well as clinical outcome.

In South Korea where a portable pump at home is not permitted, the introduction of DSX is likely to bring an improvement in the compliance rate of ICT and will improve its outcome. Nevertheless, ICER or ICUR will increase if the incremental costs due to the increased utilization overwhelm the incremental effectiveness (for details, see A Time-cost Augmented Economic Evaluation of Oral Deferasirox versus Infusional Dereroxmine for Patients with Iron Overload in South Korea Value in Health Supporting Information, Part VI at: http://www.ispor.org/Publications/value/ViHsupplementary/ViH12s3_Kim.asp).

This situation was mentioned in a study conducted in the UK [17]. The ICUR in a US study [13], reflecting the difference in the compliance rate, was higher than the ICUR in the UK study assuming compliance of the two ICTs to be 100%. The author of the UK study argued that the benefit associated with compliance should be excluded in the main analysis because the compliance benefit had not been proven. Nevertheless, to identify the benefits associated with the mode of administration, the compliance difference must be considered. Especially in South Korea, where the compliance of DFO is likely to be lower than in other countries, it will be meaningful to consider the compliance [18].

There are several limitations in this study. First, in South Korea, most patients who receive transfusions are MDS patients. Nevertheless, because of limited data, the data from patients with β-thalassaemia were used to apply the utilities for QALYs and to estimate the relationship between the compliance rate and the mortality rate. Other clinical trials reported that the efficacies of ICT were likely related to transfusional iron loading rate rather than to a disease [7]. In addition, the investigation of the utility values of MDS patients was also found to be 0.55 for DFO and 0.78 for DSX showing a difference of 0.23, which is similar to those pertaining to β-thalassaemia patients (0.24) [19]. Thus, the problem may be minor.

An exponential formula for the compliance rate and mortality rate was derived using limited data to identify the impact of compliance rate on the survival rate. Nevertheless, the goodness-of-fit was 0.999. Thus, this second limitation is likely to be minor.

Conclusion

With a considerable improvement in the convenience and saving in injection time of DSX, the results of the cost-utility analysis and the cost-effectiveness analysis of DSX versus DFO showed that DSX is a dominant therapy for patients with iron overload in South Korea. Nevertheless, a relative improvement in the compliance rate for DSX would rather have a negative effect on the economic evaluation.

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References