An economic evaluation of intravenous versus oral iron supplementation in people on haemodialysis

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Abstract

Background. Iron supplementation can be administered either intravenously or orally in patients with chronic kidney disease (CKD) and iron deficiency anaemia, but practice varies widely. The aim of this study was to estimate the health care costs and benefits of parenteral iron compared with oral iron in haemodialysis patients receiving erythropoiesis-stimulating agents (ESAs).

Methods. Using broad health care funder perspective, a probabilistic Markov model was constructed to compare the cost-effectiveness and cost-utility of parenteral iron therapy versus oral iron for the management of haemodialysis patients with relative iron deficiency. A series of one-way, multi-way and probabilistic sensitivity analyses were conducted to assess the robustness of the model structure and the extent in which the model’s assumptions were sensitive to the uncertainties within the input variables.

Results. Compared with oral iron, the incremental cost-effectiveness ratios (ICERs) for parenteral iron were $74 760 per life year saved and $34 660 per quality-adjusted life year (QALY) gained. A series of one-way sensitivity analyses show that the ICER is most sensitive to the probabilities of achieving haemoglobin (Hb) targets and the extent in which the model’s assumptions were sensitive to the uncertainties within the input variables.

Conclusions. Assuming that there is an overall increased mortality risk associated with very low Hb level (<9.0 g/dL), using parenteral iron to achieve a target Hb of 9.5 and 12 g/L is cost-effective compared with oral iron therapy among haemodialysis patients with relative iron deficiency.

Keywords: anaemia; dialysis; economic evaluation; iron deficiency

Introduction

Relative iron deficiency, defined by a total ferritin store <200 ng/mL or a percentage transferrin saturation of <20% [1], is the second most common cause of anaemia in patients with end-stage kidney disease. Approximately 20–30% of patients develop iron deficiency anaemia on dialysis [2]. Anaemia in patients on dialysis is associated with significant mortality and morbidity, leading to reduced survival and quality of life. Iron deficiency may result from poor dietary intake, decreased gastrointestinal absorption, continuous blood loss through frequent blood tests, minute gastrointestinal bleeding and haemodialysis filters [3, 4]. Not only does iron deficiency exacerbate the effects of anaemia in patients on haemodialysis, it is also responsible for the reduced and poor response to erythropoiesis-stimulating agents (ESAs), resulting in higher required doses of ESA to achieve the recommended haemoglobin (Hb) targets [5].

To date, two systematic reviews of randomized, controlled trials have assessed the comparative benefits and harms of parenteral and oral iron therapies in patients on dialysis, reporting a marginal increase in Hb levels among those who received parenteral iron [6, 7]. However, most of the reported trial data are limited by the short follow-up time and lack of major patient-centred clinical outcomes such as all-cause and cardiovascular mortality. Recommendations by international guidelines groups suggested the use of parenteral iron for haemodialysis patients because of the improved Hb response and reduction in ESA requirement compared with oral iron formulation [8, 9]. Nonetheless, morbidities such as anaphylaxis, infections and cardiovascular complications associated with iron overload and parenteral iron therapy should also be taken into consideration [10]. Given the limited availability of the longer term clinical relevant outcomes with various modalities of iron deliveries, the decision analytical model provides the next best alternative strategy to evaluate the costs and benefits of
the various routes of iron supplementation in patients with iron deficiency anaemia on dialysis. The aim of this study was to estimate the incremental health benefits and direct health care costs of parenteral iron compared with oral iron supplementation for haemodialysis patients with iron deficiency anaemia.

Materials and methods

Using a broad health care funder perspective, a probabilistic decision analytical model was developed to simulate the lifetime costs and health outcomes of a hypothetical cohort of the prevalent dialysis population ($n = 10,000$; age 18–75 years). We assumed that the cycle length was 1 year and the model terminated when all patients were deceased.

Structure of the model

The basic structure of the model is outlined in Figure 1. We first structured the model to simulate the cohort of haemodialysis patients with iron deficiency anaemia, needing either supplemental parenteral or oral iron therapy. We then populated the model using the best available evidence as clinical input estimates. Finally, we tested the uncertainties within the model’s parameter using one-way and probabilistic sensitivity analyses.

Treatment comparators

Two treatment strategies were compared: parenteral iron versus oral iron therapy among haemodialysis patients with iron deficiency. All patients were assumed to have received the standard doses of ESAs. Patients with iron deficiency could respond to supplemental iron therapy (either oral or parenteral iron), and achieve the target Hb level of 9.5–12 g/dL, leading to a 10% reduction in the standard dose of ESAs. Alternatively, they could experience poor responses to supplemental iron therapy during the annual cycle, requiring higher doses of ESA to achieve the target Hb level. Patients on supplemental iron therapy could also experience mild-to-moderate adverse effects such as constipation, nausea and abdominal discomfort, or conversely, rare but life-threatening anaphylaxis with parenteral iron therapy could also occur. The model assumed that 90% of all haemodialysis patients were treated with ESAs for the management of anaemia. The mean doses of ESAs required to attain the optimal Hb targets were based on doses used to achieve a similar target level in published randomized, controlled trials [11]. At the end of each cycle, the model accrued the effectiveness and costs of each individual in the assigned health state. Cumulative costs and benefits were calculated when the model terminated after all patients were deceased.

Input parameters for the model

Clinical data. A comprehensive literature search was performed to obtain the best available data on the treatment effectiveness and potential harms of parenteral and oral iron (Table 1). The data included the probability of side effects, the annual probability of achieving optimal Hb targets, the probability of reducing ESA doses, the risk of all-cause mortality associated with the different formulations of supplemental iron therapy in patients on dialysis. The annual average age-specific all-cause mortality estimates of dialysis patients were sourced from the Australian and New Zealand Dialysis and Transplant (ANZDATA) Registry 2000–09 [12].

Cost data. Only direct health care costs were included in the analyses (Table 2). Unit costs of all dialysis treatment modalities, ESA treatment, supplemental iron therapy (including ambulatory care costs), physician outpatient claims and other maintenance drug costs were obtained from the Australian-Refined Diagnosis Related Groups data (AR-DRG 2008–09), the Medicare Benefits Schedule (MBS 2010), the Australian Pharmaceutical Benefits Schedule (PBS) and published data from trials of ESA treatment and iron therapy [11–14]. Average Australian costs were then assigned to each of the disease health state and all costs were subsequently updated to the 2009 values using the Medicare component of the consumer price index [13]. If the cost data for treatment, adverse side effects and harms were unavailable in Australian dollars, costs from other high-income countries such as Canada, the USA and the UK were extrapolated and converted to the 2009 Australian dollars using the purchasing power parity index.

Utility data. Utility estimates are common currency of benefits used to standardize the values that people prefer or attach to different health states (Table 1). Utilities are captured on a scale between 0 and 1, where 1 represents perfect health, 0 represents death and negative values represent a health state worse than death. There were no randomized controlled trials directly comparing the quality-of-life outcomes of patients treated with parenteral and oral iron therapy. As such, the utility estimates for the average dialysis patient were sourced from previously collected utility-based quality-of-life estimates in the Australian dialysis populations. We assumed that patients who remained anaemic with Hb <9.0 g/dL had lower quality-of-life estimates compared with those who achieved an Hb level >9.0 g/dL [15, 16].

Sensitivity analysis

One-way sensitivity analysis. A series of one-way sensitivity analysis were performed to assess the robustness of results to the uncertainty surrounding the model’s estimates (Figure 2). Variables such as the probability of achieving Hb target using oral and parenteral iron, the costs of side effects using supplemental iron therapy, the relative risk of all-cause mortality...
Iron supplementation for dialysis patients

Table 1. Clinical inputs into the model

<table>
<thead>
<tr>
<th>Variables</th>
<th>Base-case values (ranges used in sensitivity analyses)</th>
<th>References</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age-specific all-cause mortality on dialysis Ages 18–44</td>
<td>0.0499</td>
<td>[12]</td>
</tr>
<tr>
<td>Ages 45–54</td>
<td>0.0797</td>
<td></td>
</tr>
<tr>
<td>Ages 55–64</td>
<td>0.1096</td>
<td></td>
</tr>
<tr>
<td>Ages 65–74</td>
<td>0.1494</td>
<td></td>
</tr>
<tr>
<td>Ages ≥75</td>
<td>0.2093</td>
<td></td>
</tr>
<tr>
<td>Male (%)</td>
<td>59.2%</td>
<td>[12]</td>
</tr>
<tr>
<td>Age distribution of the haemodialysis population (%) Ages 18–44</td>
<td>20</td>
<td>[12]</td>
</tr>
<tr>
<td>Ages 45–54</td>
<td>21</td>
<td></td>
</tr>
<tr>
<td>Ages 55–64</td>
<td>28</td>
<td></td>
</tr>
<tr>
<td>Ages 65–74</td>
<td>21</td>
<td></td>
</tr>
<tr>
<td>Ages ≥75</td>
<td>10</td>
<td></td>
</tr>
<tr>
<td>Probability of experiencing all types of side effects Oral iron</td>
<td>0.255 (0.210–0.290)</td>
<td>[6, 7]</td>
</tr>
<tr>
<td>Parenteral iron</td>
<td>0.068 (0.043–0.097)</td>
<td>[6, 7]</td>
</tr>
<tr>
<td>Probability of discontinuation of iron treatment Oral iron</td>
<td>0</td>
<td>[6, 7]</td>
</tr>
<tr>
<td>Parenteral iron</td>
<td>0.033</td>
<td>[6, 7]</td>
</tr>
<tr>
<td>Probability of reaching Hb targets using Oral iron</td>
<td>0.398 (0.251–0.405)</td>
<td>[6, 7]</td>
</tr>
<tr>
<td>Parenteral iron</td>
<td>0.630 (0.537–0.698)</td>
<td>[6, 7]</td>
</tr>
<tr>
<td>Adjusted hazard ratios of all-cause mortality by Hb levels (g/dL) &lt;9.0</td>
<td>1.74 (1.24–2.45)</td>
<td>[19, 21, 27]</td>
</tr>
<tr>
<td>9.0–&lt;10.0</td>
<td>1.25 (0.96–1.63)</td>
<td></td>
</tr>
<tr>
<td>10.0–&lt;11.0</td>
<td>1.22 (0.99–1.49)</td>
<td></td>
</tr>
<tr>
<td>11.0–&lt;12.0</td>
<td>1.0</td>
<td></td>
</tr>
<tr>
<td>12.0–&lt;13.0</td>
<td>0.90 (0.73–1.13)</td>
<td></td>
</tr>
<tr>
<td>≥13.0</td>
<td>1.04 (1.79–1.36)</td>
<td></td>
</tr>
<tr>
<td>Utility for dialysis patients with very low Hb (&lt;9.0 g/dL)</td>
<td>0.60 (0.50–0.687)</td>
<td>[15, 25]</td>
</tr>
<tr>
<td>Utility for dialysis patients with Hb – 9.0–10.0 g/dL</td>
<td>0.619 (0.54–0.692)</td>
<td>Expert opinion</td>
</tr>
<tr>
<td>Utility for dialysis patients with Hb – 10.0–12.0 g/dL</td>
<td>0.639 (0.582–0.696)</td>
<td>[15, 25]</td>
</tr>
</tbody>
</table>

mortality associated with Hb <9.0 g/dL and the percentage increase and decrease in ESA dose were assessed in the model.

Scenario analysis. Given the uncertainties in the utility-based quality-of-life estimates associated with dialysis patients receiving iron supplementation, we assumed two plausible extreme scenarios: a 10% increment and/or a 10% decrement in the quality-of-life utility estimates associated with dialysis patients who required the Hb level of 9.5–12 g/dL.

Probabilistic sensitivity analysis. We also conducted probabilistic sensitivity analysis, using varying willingness to pay thresholds, to assess the uncertainties within the model. Instead of just using point estimates for parameter values, this approach assigns a distribution to each parameter estimate and samples from that distribution using Monte Carlo simulation to estimate the expected value of each option. We used beta distributions for baseline risks and utility values and log-normal distributions for relative risks.

Model outcomes
The model included the total and incremental costs and benefits [in life years saved (LYSs) and quality-adjusted life years (QALYs) gained] of parenteral and oral iron therapy in patients on dialysis. The incremental cost-effectiveness ratio (ICER), measured in terms of costs per LYS and costs per quality-adjusted life year gained, was calculated using the following formula:

\[
\text{ICER} = \frac{\text{Cost}_{\text{parenteral}} - \text{Cost}_{\text{oral}}}{\text{Effectiveness}_{\text{parenteral}} - \text{Effectiveness}_{\text{oral}}}
\]

Future costs and benefits were discounted using a discount rate of 5% per annum, and half-cycle corrections were employed. We used TreeAge Pro Suite 2010 (TreeAge software, Williamstown, MA, USA) and Microsoft® Excel to develop and analyse the model. Ethics approval was not required for this study because it was a modelled analysis and did not utilize individual patient data, but rather, estimates from published literature were used.

Results

Base-case analysis
Table 3 shows the total and incremental costs and benefits (in life years and QALYs gained) comparing parenteral with oral iron therapy among patients of varying ages on haemodialysis with iron deficiency anaemia. Compared with oral therapy, the average gains in life years and QALYs among patients who received parenteral iron were 0.266 LYS and 0.574 QALYs, associated with an ICER of $74 760/LYS and $34 660/QALY, respectively.
One-way sensitivity analysis

The model was most sensitive to the probability of reaching Hb targets using supplemental iron therapy, the relative risk of death associated with low Hb levels (<9.0 g/L) and the extent of dose reduction and/or increase in the ESA use associated with the varying Hb levels. Figure 1 shows the variability of the ICERs with the influential variables tested over a range of plausible values in the one-way sensitivity analyses. The vertical line represents the results of the base-case analysis with an ICER of $74,764/LYS. For example, the ICER varied from $58,805/LYS to over $105,000/LYS if the ESA doses were decreased and/or increased by 10% from the standard ESA doses required by patients on haemodialysis receiving intravenous iron therapy. If the relative risk of death associated with very low Hb levels (<9.0 g/L) varied between 1.0 and 5 times greater than patients with target Hb between 9.5 and 12.0 g/L, the ICER comparing parenteral and oral iron reduced from over $200,000/LYS to less than $75,000/LYS.

Scenario analysis

Under the most favourable conditions, where there was a 10% increment (or a 0.07 increase) in utility scores...
among those who achieved a higher Hb level (9.5–12 g/dL) compared with those with a lower Hb level (<9.0 g/dL), the ICER ranged from a base-case value of $34 660/QALY to less than $10 000/QALY. Under the least favourable conditions, where there was a 10% decrement (or an absolute 0.069 decrease) in the utility scores among those who achieved a higher Hb level (9.5–12 g/dL) compared with those with a lower Hb level (<9.0 g/dL), the ICER increased to over $200 000/QALY.

Probabilistic sensitivity analysis
The scatter plots with the 95% confidence ellipses shown in Figure 3 illustrate the mean incremental costs and health outcomes, and the uncertainties surrounding the mean parameter estimates associated with parenteral and oral iron therapy among patients with iron deficiency anaemia on haemodialysis. The x-axis represents the incremental gains in quality-adjusted life years and the y-axis represents the incremental costs of comparing parenteral iron with oral iron supplements. All the scatter plots are located in the northeast (NE) quadrant of the cost-effectiveness plane, indicating that parenteral iron is more effective but also more costly than oral iron therapy among haemodialysis patients with iron deficiency anaemia. The diagonal line represents the varying willingness-to-pay threshold between $20 000/QALY to $50 000/QALY. If the willingness to pay threshold is
$20,000/QALY, <10% of the simulations fall to the right-hand side of the diagonal line, indicating that parenteral iron is only cost-effective in <10% of the time at that threshold. However, if the decision-maker is willing to pay $50,000 per QALY, then almost all (>90%) of the simulations fall to the right-hand side of the diagonal line, indicating that parenteral iron is often cost-effective compared with oral iron.

Figure 4 shows the results of the probabilistic sensitivity analyses in the form of the cost-effectiveness acceptability curve (CEAC). A CEAC shows the probability that an intervention is cost-effective compared with the alternative, given the observed data, for a range of maximum monetary values that a decision-maker might be willing to pay for a particular unit change in outcome [17]. Using our example in Figure 4, the CEAC indicates that there is a 75% likelihood that the cost-effectiveness of treating haemodialysis patients with iron deficiency anaemia using parenteral iron, compared with oral iron, is less than $40,000 per QALY gained, i.e. given a willingness to pay $40,000/QALY, the probability that parenteral iron is cost-effective compared with oral iron is 0.75.

**Discussion**

Given the current available data, our modelled analyses suggest that using parenteral iron compared with oral iron supplementation for the treatment of iron deficiency in haemodialysis patients is associated with improved clinical benefits but at the expense of extra costs. The additional expense is still well-within the scope of what is commonly considered good value for money, with an incremental cost-effectiveness ratio of less than $76,000 per additional life year in full health, and $34,660 per additional QALY gained. Using a willing-to-pay threshold of $50,000/QALY, the probability that parenteral iron is cost-effective compared with oral iron is over 90%.

Although it may be attractive to recommend parenteral iron over oral iron therapy for haemodialysis with relative iron deficiency, the base-case results are subject to substantial uncertainties and should be interpreted with caution. The observed clinical benefits are driven predominantly by the improved Hb responses and the consequent savings associated with the reduced doses of ESA. Clinicians and policy-makers should be cautious of the risk of death associated with the varying levels of Hb concentrations when making decisions about the use of supplemental iron therapy in dialysis patients with relative iron deficiency. We now have robust evidence to show that targeting higher Hb levels (>12 g/dL) in patients with CKD using ESA is associated with an increased overall mortality risk, increased risk of arteriovenous access thrombosis and uncontrolled hypertension [18–20]. However, it remains unclear as to whether the excess mortality risk is associated with the higher Hb concentrations, or due to the potential dose-dependent harmful effects of ESA in patients with CKD, or both. If indeed, ESA plays a role in the harmful causal pathway, supplementing anaemic dialysis patients with parenteral iron therapy with a concurrent dose reduction of ESA may appear to be even more favourable.

Observational data have suggested an excess risk of cardiovascular and all-cause mortality by at least 1.5- to 2-fold among dialysis patients with very low Hb levels [21]. There may be biologically plausible explanations to suggest anaemia increases the risk of death, particularly cardiovascular mortality, through impaired oxygen transport.
delivery to tissues, the consequent tissue hypoxia and subsequent end-organ dysfunction [22, 23]. However, there is a paucity of trial-based evidence to assess the direct causal relationship between anaemia correction, or the extent to which anaemia should be corrected, and the risk of mortality reduction in patients with CKD. The substantial variability and uncertainties in the model’s parameter estimates are reflected by the change in the overall ICER, in the order of 2.8- to 3-fold, when the relative risk of death associated very low Hb levels (<9.0 g/dL) were varied between the extremes of 1 to 5 times greater than those with Hb levels between 9.5 and 12.0 g/dL, in the univariate sensitivity analyses.

Our modelled analyses have also shown that quality-of-life estimates can substantially alter the cost-effectiveness ratios of our two proposed interventions. Quality-of-life adjustment appears to have a sizable impact on the overall outcome, and has led the ICER of the cost-effectiveness analysis to move across the potential ‘cost-effectiveness threshold’ of $50 000/LSY or QALY after adjusted for the effects of quality-of-life differences between interventions. Previous studies have reported that interventions for chronic illnesses which could potentially lead to a greater change in quality of life relative to the mortality effects are more likely to increase the incremental quality-adjusted life years than interventions for acute illnesses [24]. There is a lack of quality-of-life outcomes assessed in trials of different routes of iron supplementation among patients with CKD. As such, our utility estimates were sourced from published utility scores from meta-analyses of randomized, controlled trials comparing lower with higher Hb targets among dialysis patients receiving ESAs [15, 25, 26]. A 10% increase or decrease in the utility scores associated with a higher Hb level in the parenteral iron arm resulted in a 3-fold change in the overall ICER, ranging from a value of over $200 000/QALY to less than $10 000/QALY. Given the current available data, we cannot confidently assume that parenteral iron is better value for money than oral iron because of the uncertainties regarding the assumptions we made for the quality-of-life benefits associated with the higher Hb level.

To our knowledge, this is the first economic evaluation that evaluates the benefits, harms and costs of parenteral and oral iron supplementation among anaemic patients on dialysis. Our analyses are robust to the variation in costs and some of the health benefits across the different scenarios and sensitivity analyses. Using probabilistic sensitivity analyses, we have assessed the uncertainties of the influential variables simultaneously within the assigned distributions of the variables.

There are a number of limitations in our study. First, our efficacy estimates were sourced from two meta-analyses of trials of iron supplementation of CKD patients from different regions. These trials are limited by the short-term follow-up with a lack of longer term patient-relevant outcomes such as overall and cardiovascular mortality. As such, mortality and survival estimates were extrapolated from the Australian and New Zealand dialysis cohorts. It is likely that the survival outcomes will vary across different health care settings and may not necessarily be generalizable to the region of interests. Secondly, we have not directly valued the quality-of-life implications associated with the adverse effects of the different modes of iron supplementation, such as the gastrointestinal symptoms associated with oral iron therapy. The experience of having side effects from an intervention is likely to impact on the incremental gain in QALYs relative to the gains in the number of life years. In addition, we have not accounted for the variability in the standard doses of ESA that may exist between different settings. We have also not taken into consideration the variability of the different types and doses of iron formulations in the model. It is possible that modest doses of intravenous iron are beneficial, whereas large doses may be harmful. Finally, we have not considered the indirect costs such as productivity losses due to the time loss to work for outpatient care.

Implications for policy and future research

A well-powered, large-scale, randomized, controlled trial comparing parenteral and oral iron therapy in patients with CKD and iron deficiency anaemia with pre-specified longer term patient-relevant outcomes such as quality-of-life benefits, costs, cardiovascular and overall mortality are needed to answer the current evidence gaps in clinical practice. In-depth qualitative research should also be conducted in an effort to ascertain patient preferences for their iron management and to determine what factors are important to patients such as side effects and affects the quality of life when undertaking iron supplementation. Given the small differences in clinical outcomes between parenteral iron and oral iron and the uncertainties around the clinical estimates of clinical efficacy, individual iron protocols should take into account patient preferences when implementing an iron management regime for individual patients.

Conclusions

Based on the results of the current trial-based and observational data, our modelled analyses suggest that parenteral iron compared with oral iron therapy may improve the survival, the quality of life and is cost-effective for dialysis patients with relative iron deficiency.

Conflict of interest statement. None declared.

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