TITLE: Ferumoxytol versus Other Intravenous Iron Therapies for Anemia: A Review of the Clinical and Cost-effectiveness and Guidelines

DATE: 7 June 2013

CONTEXT AND POLICY ISSUES

Anemia, particularly iron deficiency anemia, is a common complication in patients with end stage chronic kidney disease (CKD, stage 3-5 disease and those on dialysis).\(^1,2\) CKD patients have a deficiency in endogenous erythropoietin (a hormone that stimulates the production of red blood cells) often requiring supplementation with erythropoiesis-stimulating agents (ESA), which results in increased utilization of iron, depleting iron stores.\(^2,3\) Additionally CKD patients have reduced iron intake, compromised gastrointestinal iron absorption and bleeding (including blood loss during the dialysis process).\(^2,4\)

Evidence suggests that intravenous (IV) iron is preferred to oral for patients receiving ESA therapy and undergoing dialysis. For non-dialysis patients there is insufficient evidence to suggest the preferential use of IV formulations, therefore oral therapy should be tried first and IV iron used if there is an inadequate response or the patient cannot tolerate oral therapy.\(^4-6\)

Ferumoxytol (Feraheme) is an intravenous iron formulation available in Canada for the treatment of iron deficiency anemia (IDA) in adults with CKD.\(^7\) Ferumoxytol is a superparamagnetic iron oxide, and is coated with a carbohydrate shell which isolates the iron from plasma components following injection.\(^1\) The iron is then taken up by macrophages in the liver, spleen and bone marrow where it is released from its carbohydrate shell and either stored or transported for incorporation into hemoglobin during erythropoiesis—the formation of red blood cells.\(^1,8\)

Alternative intravenous iron preparations approved for use in Canada include iron sucrose, iron dextran and sodium ferric gluconate.\(^9-11\) IV iron has been long used for replenishing body stores but is not free of adverse effects, concerns being susceptibility to infection, hypersensitivity reactions, and possible direct cellular toxicity. In order to minimize potential adverse effects, limited quantities of iron per dose are given via slow IV injections or infusions, requiring multiple doses to replete iron stores, thereby increasing hospital costs and causing inconvenience to patients.\(^4\) Iron dextran and sucrose are commonly given in doses of 100 mg and CKD patients normally require a minimum of 500 mg to replenish stores.\(^4\) There is some experience in

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administration of iron sucrose 500 mg via an IV infusion over 3.5 to 4 hours on day 1 and 14, however hypotension occurred in 2 of 30 of the trialed patients. Anaphylactic reactions are seen with iron dextran, necessitating a test dose prior to the first therapeutic dose followed by observation of the patient for one hour; the infusion can then be administered over 1 to 3 hours. Sodium ferric gluconate is frequently administered at doses of 125 mg IV over one hour, alternatively it can be administered as a slow IV injection at 12.5 mg/min (over 10 min for a 125 mg dose).

Ferumoxytol was approved for use following two open label randomized controlled trials comparing it to oral iron in patients with CKD and one study in patients with hemodialysis – dependent CKD. Ferumoxytol was designed to allow higher doses to be administered by rapid IV injection and does not require a test dose. Ferumoxytol 510 mg of elemental iron is administered IV at a rate of 30 mg per second. Patients must however be observed for 30 min following the injection and may receive a second dose in 2 to 8 days.

This report will review the comparative efficacy, safety and cost-effectiveness data of ferumoxytol relative to the alternative IV iron preparations available in Canada. It will also review evidence based guidelines for the use of ferumoxytol.

RESEARCH QUESTIONS

1. What is the clinical effectiveness and safety of ferumoxytol compared with other intravenous iron therapies for adult patients with anemia resulting from chronic kidney disease or other types of anemia?

2. What is the cost-effectiveness of ferumoxytol compared with other intravenous iron therapies for adult patients with anemia?

3. What are the evidence-based guidelines regarding the use of ferumoxytol for adult patients with anemia?

KEY FINDINGS

Limited evidence from studies with methodological issues suggests that ferumoxytol seems to have comparable efficacy and higher adverse events compared with other available IV iron preparations. No Canadian data on cost-effectiveness or evidence-based guidelines for the use of ferumoxytol were identified.

METHODS

Literature Search Strategy

A limited literature search was conducted on key resources including Pubmed, Embase, The Cochrane Library (2013, Issue 3), University of York Centre for Reviews and Dissemination (CRD) databases, Canadian and major international health technology agencies, as well as a focused Internet search. No methodological filters were applied. Where possible, retrieval was limited to the human population. The search was also limited to English language documents published between January 1, 2008 and May 9, 2013.
Selection Criteria and Methods

One reviewer screened citations to identify publications that met the inclusion criteria. Potentially relevant articles were retrieved based on the review of titles and abstracts. Full-text articles were considered for inclusion based on the selection criteria listed in Table 1.

Table 1: Selection Criteria

<table>
<thead>
<tr>
<th>Population</th>
<th>Adults with anemia</th>
</tr>
</thead>
<tbody>
<tr>
<td>Intervention</td>
<td>Ferumoxytol</td>
</tr>
<tr>
<td>Comparator</td>
<td>Other intravenous iron products; iron sucrose, iron dextran, sodium ferric gluconate</td>
</tr>
<tr>
<td>Outcomes</td>
<td>Q1: clinical benefits and harms</td>
</tr>
<tr>
<td></td>
<td>Q2: cost-effectiveness</td>
</tr>
<tr>
<td></td>
<td>Q3: any evidence-based guidelines that include ferumoxytol</td>
</tr>
<tr>
<td>Study Designs</td>
<td>Health technology assessment (HTA), systematic review, meta-analysis</td>
</tr>
<tr>
<td></td>
<td>Randomized controlled trial (RCT)</td>
</tr>
<tr>
<td></td>
<td>Non-randomized study</td>
</tr>
<tr>
<td></td>
<td>Economic evaluation</td>
</tr>
<tr>
<td></td>
<td>Guideline</td>
</tr>
</tbody>
</table>

Exclusion Criteria

Articles were excluded if they did not satisfy the selection criteria. Articles which were available only as abstracts were excluded.

Critical Appraisal of Individual Studies

A critical appraisal of the study methods could not be conducted as one study\textsuperscript{12} was an analysis of spontaneously reported adverse events and one\textsuperscript{13} was an assessment with few methodological details reported. Instead limitations of these studies are discussed.

SUMMARY OF EVIDENCE

Quantity of Research Available

The literature search yielded 422 citations. Upon screening titles and abstracts, 402 citations were excluded and 20 potentially relevant articles were retrieved for full-text review. Two additional potentially relevant reports were retrieved from the grey literature and one abstract of an unpublished trial was found by scanning references of relevant articles. Of the 23 potentially relevant reports 21 were excluded. One analysis of reported adverse events among patients receiving IV iron and one assessment of ferumoxytol by the Scottish Medicines Consortium. met the inclusion criteria.\textsuperscript{12,13} The assessment appeared to be an HTA but had few details reported and it was unclear if a systematic approach was used. No systematic reviews or RCTs met the inclusion criteria. No evidence-based clinical practice guidelines were identified that included recommendations for ferumoxytol. The process of study selection is outlined in the PRISMA flowchart (Appendix 1).
References of articles of potential interest which did not meet the inclusion criteria are included in Appendix 2.

**Summary of Study Characteristics**

In 2012, Bailie GR et al. analyzed reported adverse events (AEs) among patients using IV iron products. Data was obtained on adverse effects spontaneously reported to the FDA from October 2009 to June 2010 for iron sucrose, sodium ferric gluconate, iron dextran and ferumoxytol. AEs were classified into four categories and event counts were totaled within each category. Rates of adverse events were then compared. Because IV iron products are supplied in different sizes, dosing was standardized by converting to 100 mg dose equivalents. Rates were also calculated as rates per units of product sold thereby estimating the patient exposure to IV iron. Adverse event (AE) categories were death, serious AE (i.e., resulting in hospitalization, disability, pulmonary embolism, anaphylaxis, unresponsiveness, or loss of consciousness or otherwise considered life-threatening), other major AE (i.e., resulting in circulatory collapse, hypotension, anaphylactoid reaction, dyspnea, pruritus, hypersensitivity, or urticaria), and other AE (i.e. nonallergic events).

The Scottish Medicines Consortium (SMC) has completed an assessment of ferumoxytol and provided advice for its use in Scotland. The comparative efficacy and safety of ferumoxytol compared to oral iron was summarized. A mixed treatment comparison (MTC) was provided to the SMC by the manufacturer and discussed in the report. The goal of the MTC was to provide additional comparative data with IV iron preparations (iron sucrose, ferric carboxymaltose, cideferron, iron dextran, ferric gluconate) in patients with CKD. The MTC was discussed briefly, but specific details were not provided. The primary endpoint was change in hemoglobin from baseline. Eighteen studies of various IV iron preparations versus oral iron (except one study which compared two IV preparations) were included. Two additional MTCs were completed, one that included studies with a duration of ≤ 60 days and one that evaluated change in ferritin from baseline.

The SMC report included a cost-minimization analysis. The cost minimization analysis, based on the aforementioned MTC results was provided by the manufacturer. The time horizon was 5 weeks, and ferumoxytol was compared with other IV iron preparations in the treatment of IDA in adults with CKD not on dialysis in whom oral iron was ineffective or could not be used. Costs to deliver 1g of elemental iron were analyzed and included drug acquisition costs, nursing time, equipment, and hospital transportation.

**Summary of Critical Appraisal**

A critical appraisal of the studies could not be conducted as one was an analysis of spontaneously reported adverse events and one was an assessment with few details. Instead limitations of these studies are discussed later in the limitations section.

**Summary of Findings**

The report by Bailie et al. evaluated 197 reports of AEs. Of the 197 reports, 44.7% cited ferumoxytol, 24.9% cited iron sucrose, 10.7% cited sodium ferric gluconate and 19.8% cited iron dextrose. The rates of reported AEs per million units sold were 745.76 for ferumoxytol, 5.25 for iron sucrose, 6.85 for sodium ferric gluconate, and 27.08 for iron dextrose. The rates of reported
AEs per million 100-mg dose equivalent were 146.67 ferumoxytol, 5.24 for iron sucrose, 10.99 for sodium ferric gluconate, and 27.46 for iron dextrose. Details are provided in Appendix 3.

The SMC assessment reported that the results of the company provided MTC support the assumption of equivalent efficacy outcomes for ferumoxytol in comparison with alternative IV iron.13 Perceived benefits of ferumoxytol discussed included: improved convenience and compliance because of less required injections and reduced treatment duration.

The cost-minimization analysis provided by the manufacturer stated that ferumoxytol was the preferred treatment on cost-minimization grounds.13

Ferumoxytol was accepted for restricted use within NHS Scotland for IV treatment of IDA in adult patients with CKD. The restriction was treatment when oral iron preparations are ineffective or cannot be used.13

LIMITATIONS

Evidence available for comparison of ferumoxytol with other IV iron therapies was limited.

The results of the analysis of reported adverse events of IV iron products12 must be interpreted in light of the following: This type of analysis may provide us with information on the real world post marketing use of ferumoxytol, it is hypothesis generating and not intended to guide decisions as it is subject to many limitations warranting cautious interpretation. Reporting bias is the main concern in this type of analysis. Patient characteristics were not discussed hence it is difficult to determine the generalizability of the findings. A potential bias may exist in that patients that are receiving iron sucrose which has been on the market for some time are likely doing well and free from harm, while patients receiving ferumoxytol may have been prescribed it because it is a newly available medication and they have been unable to tolerate previously tried iron preparations and hence more likely to experience an AE. Also, patients worse off/more symptomatic may receive the IV alternative that allows a larger dose to be given at once (ferumoxytol allows administration of 510 mg of elemental iron given in one dose) and this could potentially bias findings. There is potential of confounding from the “Weber effect”. The “Weber effect” is a phenomenon related to the fact that there is a tendency to report adverse events of new medications relative to other alternatives that may have been available longer. Ferumoxytol became available in the US in June of 2009 and collection of AE reports was initiated October 2009.

The SMC assessment13 lacked specific details of the manufacturer provided MTC and cost-minimization analysis, hence findings need to be interpreted with caution. The MTCs included in the assessment have limitations. There were variations in the dose regimens for oral and IV iron preparations in the comparative studies. Adverse events were not included in the MTC hence comparative safety was not addressed. The cost-minimization analysis may not be representative of Canadian costs.

CONCLUSIONS AND IMPLICATIONS FOR DECISION OR POLICY MAKING

There was limited evidence on the comparison of ferumoxytol with other IV iron therapies.

From AEs reported to FDA during a 9 month period commencing 3 months after ferumoxytol came to the US market, it appeared that ferumoxytol is associated with higher rate of AEs
compared with iron sucrose, sodium ferric gluconate or iron dextran. These findings need to be interpreted with caution as they were based on spontaneously reported AEs and may not capture all AEs that occurred. Also cases where there were no adverse events are not known. MTC analysis conducted by the manufacturer suggested similar efficacy for ferumoxytol versus the other IV iron preparations. A cost minimization analysis from Scotland and conducted by the manufacturer suggested that ferumoxytol appeared to be the preferred IV iron replacement therapy on cost-minimization grounds. These findings need to be interpreted with caution as this report was difficult to appraise due to lack of details.

An RCT for which a poster abstract was available suggested that ferumoxytol demonstrated comparable efficacy and a favorable safety profile relative to iron sucrose. This article was excluded as it was presented solely in abstract form. A summary is provided in Appendix 2. Definitive conclusions from this study need to await peer-reviewed publication of full study details. No evidence based guidelines specific to ferumoxytol were identified.
REFERENCES


13. Ferumoxytol, 30mg/ml solution for injection (Rienso) SMC No. (833/13) [Internet]. Glasgow: Scottish Medicines Consortium; 2013 Jan 11. [cited 2013 May 16]. Available
APPENDIX 1: Selection of Included Studies

422 citations identified from electronic literature search and screened

402 citations excluded

20 potentially relevant articles retrieved for scrutiny (full text, if available)

3 potentially relevant reports retrieved from other sources (grey literature, hand search)

23 potentially relevant reports

21 reports excluded:
- irrelevant intervention (5)
- irrelevant comparator (1)
- irrelevant outcomes (1)
- case reports (2)
- other (review articles, editorials, abstracts) (12)

2 reports included in review
APPENDIX 2: Additional References of Potential Interest

Relevant study for which only the poster abstract was identified:


A summary of the abstract is provided here. Ferumoxytol has been compared to iron sucrose in the FIRST trial by Macdougall et al. In this randomized, open label study ferumoxytol 1.02 g IV (2 injections of 510 mg) was compared with iron sucrose (100mg IV on 10 consecutive dialysis sessions for hemodialysis patients, or 200 mg IV at five non-consecutive visits over 14 days for non-hemodialysis patients) in 162 patients with CKD. Approximately 43% of patients were on dialysis. To be included patients had to have a hemoglobin measurement of less than 110 g/L and a transferrin saturation of less than 30%. Patients were excluded if they had a history of an allergy to IV iron or if their hemoglobin was <70 g/L. The primary objective of the study was to evaluate safety, therefore the efficacy analysis was exploratory and should be interpreted with caution. The mean change in hemoglobin from baseline to week 5 was 7.1 g/L for ferumoxytol (n=80) and 6.1 g/L for iron sucrose (n=82). Adverse events were analyzed and 48% of patients in the ferumoxytol arm experienced an adverse event compared to 65% of patients in the iron sucrose arm. The authors concluded that ferumoxytol demonstrated comparable efficacy and a favorable safety profile relative to iron sucrose.

References for case reports of potential interest:


Reference for a horizon scanning report of potential interest:

4. NIHR Horizon Scanning Centre. Ferumoxytol (Feraheme) for iron deficiency anaemia not associated with chronic kidney disease - first or second line. Birmingham (UK): The Centre; 2013.
APPENDIX 3: Main Study Findings and Authors’ Conclusions

<table>
<thead>
<tr>
<th>First Author, Publication Year</th>
<th>Main Study Findings</th>
<th>Authors’ Conclusions</th>
</tr>
</thead>
<tbody>
<tr>
<td>Bailie, 201212</td>
<td>197 AE reports 14.1 reports per million units of iron sold 15 deaths (n=6 ferumoxytol, n=5 iron dextran) 119 serious AEs (n=70 ferumoxytol) 48 other major AEs 15 other AEs Of the 197 reports: 24.9% cited iron sucrose 44.7% cited ferumoxytol 10.7% cited sodium ferric gluconate 19.8% cited iron dextran Sales: Highest for iron sucrose (67%) Sodium ferric gluconate (22%) Iron dextran (10%) Lowest for ferumoxytol (0.9%)</td>
<td>“Analysis of reports submitted to FDA revealed large differences among IV iron products in reported deaths, serious AEs, other major AEs and other AEs. Iron sucrose and sodium ferric gluconate were associated with much lower rates of AEs per million units sold than iron dextran or ferumoxytol, which were associated with the highest rates of all reported AE classifications.” pg. 319</td>
</tr>
</tbody>
</table>

Rates of AE reported per million units sold

<table>
<thead>
<tr>
<th>Product</th>
<th>All AE</th>
<th>Death</th>
<th>SAE</th>
<th>Other major AE</th>
<th>Other AE</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ferumoxytol</td>
<td>745.76</td>
<td>50</td>
<td>583.3</td>
<td>83.3</td>
<td>16.67</td>
</tr>
<tr>
<td>Iron sucrose</td>
<td>5.25</td>
<td>0.11</td>
<td>2.25</td>
<td>1.82</td>
<td>1.07</td>
</tr>
<tr>
<td>Sodium ferric gluconate</td>
<td>6.85</td>
<td>0.33</td>
<td>4.92</td>
<td>0.98</td>
<td>0.66</td>
</tr>
<tr>
<td>Iron dextran</td>
<td>27.08</td>
<td>4.86</td>
<td>9.02</td>
<td>12.5</td>
<td>0.69</td>
</tr>
</tbody>
</table>

Rates of AE per million 100-mg dose equivalents (DEq) of IV iron

<table>
<thead>
<tr>
<th>Product</th>
<th>All AE</th>
<th>Death</th>
<th>SAE</th>
<th>Other major AE</th>
<th>Other AE</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ferumoxytol</td>
<td>146.67</td>
<td>10</td>
<td>116.67</td>
<td>16.67</td>
<td>3.33</td>
</tr>
<tr>
<td>Iron sucrose</td>
<td>5.24</td>
<td>0.11</td>
<td>2.24</td>
<td>1.82</td>
<td>1.07</td>
</tr>
<tr>
<td>Sodium ferric gluconate</td>
<td>10.99</td>
<td>0.52</td>
<td>7.85</td>
<td>1.57</td>
<td>1.05</td>
</tr>
<tr>
<td>Iron dextran</td>
<td>27.46</td>
<td>4.93</td>
<td>9.15</td>
<td>12.68</td>
<td>0.70</td>
</tr>
</tbody>
</table>

AE= adverse event, SAE= serious adverse event