TITLE:  Erythropoiesis Stimulating Agents in Chronic Kidney Disease: Clinical Effectiveness and Guidelines

DATE:  12 March 2015

RESEARCH QUESTIONS

1. What are the clinical benefits and harms of erythropoiesis stimulating agents in the treatment of patients with chronic kidney disease and hemoglobin ≥100 g/L?

2. What are the evidence-based guidelines for erythropoiesis stimulating agents in the treatment of patients with chronic kidney disease and hemoglobin ≥100 g/L?

KEY FINDINGS

Two systematic reviews, one randomized controlled trial reported in two publications, and two evidence-based guidelines were identified regarding erythropoiesis stimulating agents in chronic kidney disease.

METHODS

A limited literature search was conducted on key resources including PubMed, The Cochrane Library (2015, 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. Methodological filters were applied to limit retrieval to health technology assessments, systematic reviews, meta-analyses, randomized controlled trials, and guidelines. Where possible, retrieval was limited to the human population. The search was also limited to English language documents published between January 1, 2010 and March 4, 2015. Internet links were provided, where available.

The summary of findings was prepared from the abstracts of the relevant information. Please note that data contained in abstracts may not always be an accurate reflection of the data contained within the full article.
SELECTION CRITERIA

One reviewer screened citations and selected studies based on the inclusion criteria presented in Table 1.

Table 1: Selection Criteria

<table>
<thead>
<tr>
<th>Population</th>
<th>Patients with CKD and Hb ≥100 g/L with no symptoms of anemia</th>
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</thead>
<tbody>
<tr>
<td>Intervention</td>
<td>ESAs</td>
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<tr>
<td>Comparator</td>
<td>Delayed ESAs</td>
</tr>
<tr>
<td></td>
<td>Other therapies</td>
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<tr>
<td>Outcomes</td>
<td>Clinical effectiveness (benefits [normalize Hb levels, survival] and harms)</td>
</tr>
<tr>
<td></td>
<td>Guidelines</td>
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<tr>
<td>Study Designs</td>
<td>Health technology assessment reports, systematic reviews, meta-analyses, randomized controlled trials, evidence-based guidelines</td>
</tr>
</tbody>
</table>

CKD = chronic kidney disease; ESA = erythropoiesis stimulating agents; Hb = hemoglobin.

RESULTS

Rapid Response reports are organized so that the higher quality evidence is presented first. Therefore, health technology assessment reports, systematic reviews, and meta-analyses are presented first. These are followed by randomized controlled trials and evidence-based guidelines.

Two systematic reviews, one randomized controlled trial reported in two publications, and two evidence-based guidelines were identified regarding erythropoiesis stimulating agents (ESAs) in chronic kidney disease (CKD). No relevant health technology assessments were identified. Of note, because anemia can be asymptomatic, references where it was stated that patients had anemia but where symptom status was unclear were included in this report.

Additional references of potential interest are provided in the appendix.

OVERALL SUMMARY OF FINDINGS

Two systematic reviews\(^1,2\), one randomized controlled trial reported in two publications,\(^3,4\) and two evidence-based guidelines\(^5,6\) were identified regarding ESAs in CKD.

One systematic review\(^1\) of randomized trials examined the potential effects of targeted hemoglobin (Hb) levels (high Hb, approximately 13.0 g/dL; low Hb, approximately 10.0 g/dL) on clinical outcomes in CKD patients with anemia who were treated with ESAs. The authors reported a statistically significant increased risk of mortality, hospitalization, stroke, and hypertension with high Hb levels, but no increased risk in non-fatal myocardial infarction and renal replacement therapy. The authors concluded that targeting low Hb levels was beneficial to CKD patients, with this benefit being greater in the pre-dialysis population.\(^1\) Another systematic review and meta-analysis\(^2\) of randomised controlled trials, which allocated patients to different ESA doses, reported that higher Hb targets were associated with increased risk of vascular access thrombosis and stroke. No impacts of higher Hb targets were observed on end-stage renal disease or all-cause mortality.\(^2\)

The identified randomized controlled trial\(^3\) examined the effects of maintaining high Hb on renal function in patients with CKD who were not on dialysis. Patients were randomized to either a
high Hb group (Hb equal to 11.0 g/dL through 13.0 g/dL) receiving darbepoetin alfa or a low Hb group (Hb equal to 9.0 g/dL through 11.0 g/dL) with epoetin alfa. Three-year cumulative renal survival rates were higher in the high Hb group compared with the low Hb group (39.9% versus 32.4%, respectively) although this difference was not statistically significant. Lower event rates were observed in the high Hb group; however, there were no between-group differences in the incidence of serious adverse cardiovascular events and no safety issues were noted in either group. In a separate publication of the same trial, the authors reported a statistically significantly greater impact on quality of life in the high Hb group. In addition, a statistically significant decrease in the left ventricular mass index was observed in the high Hb group, while this index remained stable in the low Hb group.

The guideline by Kidney Disease: Improving Global Outcomes (KDIGO) Anemia Work Group recommends that ESA therapy not be initiated for adult CKD (non-dialysis) patients with an Hb concentration of ≥10.0 g/dL. In addition, the decision of whether to initiate ESA therapy for patients with Hb concentrations <10.0 g/dL should be individualized and based on multiple factors that are individual to the patient (e.g. the rate of fall of Hb concentration, response to previous iron therapy, transfusion risk, associated ESA therapy risks, and the presence anemia symptoms). For Stage five CKD patients, ESA therapy should be used to avoid having Hb levels fall below 9.0 g/dL to 10.0 g/dL. For pediatric patients, the Hb level at which ESA therapy is initiated should consider potential benefits and harms. One ungraded recommendation from the KDIGO guideline also states that individualized therapy should be considered and that ESA therapy could be started above 10.0 g/dL. The United Kingdom Renal Association guideline recommends the following for determining the initial ESA dose: the patient’s Hb level, Hb target levels, the rate of increase in the Hb level, and various clinical circumstances. This guideline does not provide parameters for patient and target Hb levels.
REFERENCES SUMMARIZED

Health Technology Assessments
No literature identified.

Systematic Reviews and Meta-analyses


Randomized Controlled Trials


Guidelines and Recommendations


APPENDIX – FURTHER INFORMATION:

Non-Randomized Studies


Clinical Practice Guidelines – Unclear Methodology

   See: Anemia, pages 37-38


Position Statement


Review Articles
