Systematic review of the impact of erythropoiesis-stimulating agents on fatigue in dialysis patients

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Abstract

Background. One of the cardinal symptoms of anemia in chronic kidney disease (CKD) patients is fatigue. Recently, results from Trial to Reduce Cardiovascular Events with Aranesp Therapy (TREAT) raised questions about the role of erythropoiesis-stimulating agents (ESAs) in improving fatigue and the appropriate hemoglobin (Hb) target in anemic patients with CKD. These discussions should be considered with all available evidence to determine the level of benefits and risks associated with ESA therapy on fatigue among both early-stage CKD patients and end-stage renal disease patients on dialysis.

Methods. The study was a systematic review of the literature on fatigue in adults on maintenance dialysis therapy. The requirement for inclusion in the review was the measurement of fatigue before and after ESA treatment. Outcomes that were assessed were fatigue as measured by the Kidney Disease Questionnaire, the 36-item Short-Form general health survey, the Nottingham Health Profile, the Profile of Mood States or the Functional Assessment of Chronic Illness Therapy-Fatigue scale. Several different measures of fatigue were used in the studies.

Results. Fifteen articles met the criteria for inclusion, including 10 distinct studies and one extension study. There was one placebo-controlled randomized clinical trial (RCT) and one extension, five single-arm, three high versus low, one intravenous versus subcutaneous and one switch from epoetin alfa to darbepoetin alfa. The only placebo-controlled RCT found a 22–26% improvement in fatigue. Single-arm cohort studies demonstrated a reduction in fatigue after a substantial increase in Hb. Studies with a baseline Hb <10 g/dL and partial correction to a minimum Hb ≥10 g/dL showed an average improvement in fatigue of 34.6%. Studies with a baseline Hb ≥11 g/dL and full correction to a minimum Hb ≥12 g/dL showed an average improvement in fatigue of 5.5%, while studies with no change in Hb (either placebo or control group) showed a decline of 0.7% in fatigue outcomes.

Conclusion. Partial correction of anemia with ESA results in improvement of fatigue among patients on dialysis, most strikingly in those patients with baseline Hb levels <10 g/dL.

Keywords: anemia; dialysis; ESA; fatigue; hemoglobin

Introduction

Anemia occurs commonly in patients with chronic kidney disease (CKD). It is most pronounced in patients with end-stage renal disease (ESRD) requiring dialysis and has been reported to be associated with a variety of symptoms including fatigue, muscle weakness, impaired physical functioning, shortness of breath and depression [1].

Patient perception of fatigue has been noted to be a highly important problem for patients with CKD [2]. Fatigue symptoms have been associated with increased morbidity and mortality in these patients [3]. In this population, fatigue may be multifactorial in etiology, but anemia has been noted to be associated with the presence of fatigue among patients with and without CKD [4, 5]. Additionally, fatigue has been recognized as a core symptom of anemia by numerous organizations such as the US National Heart, Lung and Blood Institute, the National Kidney Foundation, the National Anemia Action Council and the Renal Support Network [6–9]. Furthermore, in qualitative research studies, decreased ‘energy’ and feeling ‘tired’ are among the most common of patient quotes when describing their anemia symptoms [1].

Erythropoiesis-stimulating agents (ESAs) are the mainstay of therapy used to improve hemoglobin (Hb) levels in this population, and treatment of anemia has been shown to have a beneficial effect on certain aspects of health-related quality of life (HRQOL) in ESRD patients. Two recent systematic reviews, one in CKD on dialysis and another in the setting of non-dialysis CKD, suggested that the partial correction of anemia resulted in consistent and positive improvements in both patient- and physician-assessed...
physical functioning [10, 11]. For example, the meta-
alysis conducted among CKD patients on dialysis
showed that there was a 24% increase in VO\textsubscript{2} peak (oxygen
consumption per minute at the peak workload at the test)
from before to after ESA therapy. This improvement trans-
lated into a significant improvement in patient-reported
assessments of physical functioning measured by the Sick-
ness Impact Profile indicating a 24–62% improvement in
physical activities and functioning after ESA therapy in
the placebo-controlled randomized clinical trial (RCT) [12].
In addition, the systematic review conducted among CKD
patients not on dialysis also showed improved energy and
fatigue after treatment of anemia with ESAs, but changes in
fatigue and energy have not yet been summarized similarly
among patients on dialysis [11].

Recently, an RCT, albeit in CKD patients not on dial-
sysis, has shown only moderate effects of ESA therapy on
fatigue assessed by the Functional Assessment of Cancer
Therapy-Fatigue Scale (FACT-Fatigue) [13]. Additionally,
multiple studies have raised questions concerning the ap-
propriate Hb target for therapy in CKD patients [13–16].

The purpose of the present study was to investigate the
potential impact of the treatment of anemia with ESA ther-
apy on patient perception of fatigue in dialysis patients. A
comprehensive literature review was undertaken and all
relevant articles were evaluated.

**Methods**

**Review strategy**

We designed and completed a systematic review of the literature on
the impact of ESAs on fatigue outcomes in patients with ESRD. A systematic
search was conducted using MEDLINE and EMBASE. The literature search
was limited to papers published in the English language through 30 June
2010. Search terms for kidney disease included ‘chronic renal failure’,
‘chronic renal insufficiency’, ‘kidney failure, chronic’ [MeSH], ‘renal insuf-
fiency, chronic’ [MeSH], ‘end-stage renal disease’, ‘dialysis’, ‘hemodialy-
sis’ and ‘haemodialysis’; for ESAs the search terms were as follows ‘erythropoetin, recombinant’ [MeSH], ‘epoetin alfa’ [MeSH], ‘erythropoeti-
tin’ [MeSH], ‘erythropoietin beta’, ‘epoetin delta’, ‘darbepoe-
less’, ‘exhaustion’ and ‘lethargy’. Articles were originally identified for the
review if they met the following inclusion criteria: (i) adults with ESRD
were included. The measure was initially validated in 50 cancer patients with
fatigue assessed by the Functional Assessment of Cancer
Therapy-General (FACT-G) measure to which fatigue subscales
were added. The measure was developed based on the core Functional Assessment
of Cancer Therapy-General (FACT-G) measure to which fatigue subscales
were added. The measure was initially validated in 50 cancer patients with
Hb levels ranging from 7 to 15.9 g/dL [26]. Higher scores indicate
improved fatigue.

**Fatigue instruments**

For the review of fatigue outcomes, studies were included if participants
were assessed with one or more patient-reported outcome (PRO) measures
that included a fatigue, energy or vitality domain. The most frequently
used measures of fatigue were the Kidney Disease Questionnaire (KDQ)
[17] and the 36-item Short-Form general health survey (SF-36) [18]. The
Nottingham Health Profile (NHP) energy [19] was used in two studies; the
Profile of Mood States (POMS) fatigue [20] and the Functional Assess-
ment of Chronic Illness Therapy-Fatigue scale (FACT-Fatigue) [21] were
used in one study each.

The KDQ consists of 26 questions grouped into five domains: physical
symptoms, fatigue, depression, relationship with others and frustration
[17]. The fatigue scale consists of six questions rated on a 7-point Likert-
type scale (all of the time to none of the time). The recall period is the past
2 weeks. Higher KDQ fatigue scores indicate better function. The KDQ’s
content and construct validity and reliability have been demonstrated in a
dialysis population [18].

The SF-36 is a generic health status measure that includes eight do-
 mains: physical functioning, role-physical, bodily pain, general health,
vitality, social functioning, role-emotional, mental health and a single
health transition item [18]. There is good evidence supporting the reliabil-
ity and validity of the SF-36 in general and chronic disease populations,
including ESRD [22]. Only the vitality domain of the SF-36 was utilized in
this analysis. The vitality domain includes four items and higher scores
indicate more vitality and energy.

The NHP (Part I) is a 38-item generic health status instrument that
includes six dimensions: pain, physical mobility, sleep, emotional reac-
tions, energy and social isolation [23, 24]. It was originally developed to
be used in primary care settings in Europe but has subsequently been used
in health surveys and clinical trials. The measure has considerable content
validity across patients; however, its validity testing is somewhat limited
when compared to the SF-36. Only the NHP energy scale was used in this
analysis. The energy scale includes three items with lower scores indicating
improved energy.

The POMS covers six dimensions: tension–anxiety, depression–dejection,
anger–hostility, vigor, fatigue–inertia and confusion–bewilderment [20]. Its
validation has focused mainly on psychiatric conditions, but it has been used
in other areas such as clinical trials addressing chronic pain [25]. Only the
seven-item fatigue scale was used in this analysis. Lower scores indicate
improved fatigue.

The FACT-Fatigue covers five areas: physical well-being, social/family
well-being, emotional well-being, functional well-being and additional con-
cerns. The measure was developed based on the core Functional Assessment
of Cancer Therapy-General (FACT-G) measure to which fatigue subscales
were added. The measure was initially validated in 50 cancer patients with
Hb levels ranging from 7 to 15.9 g/dL [26]. Higher scores indicate less
fatigue.

**Information synthesis**

The content of relevant articles was summarized, including first author and
date of publication, study type, sample size, instrumentation, Hb target and
duration of follow-up. Outcomes were reported as percentage change from
baseline and where possible effect sizes were calculated. However, be-
cause the study designs (e.g. placebo controlled versus a comparison of
low target to high target versus a comparison of intravenous to subcuta-
neous injection) and follow-up time in these studies were variable, a meta-
analysis could not be conducted. We summarized the study results based
on fatigue instrument. We then synthesized all the studies that reported
both baseline Hb, achieved Hb and change in Hb as well as the improve-
ments in fatigue score. Study results were summarized to evaluate the data
points of interest, including baseline Hb level, achieved Hb level and the

![Fig. 1. Articles reviewed.](image-url)
change in fatigue score. Study results were also summarized to describe the magnitude of PRO change based on the degree of Hb change relative to baseline Hb levels. Categories include (i) mean change in Hb ≥ 1 g/dL when baseline mean Hb is <10 g/dL; (ii) mean change in Hb ≥ 1 g/dL when baseline mean Hb is ≥10 g/dL; and (iii) no increase (<1 g/dL) in Hb.

Results

Ninety potential articles were identified using the search strategy described, and abstracts of all were reviewed (Figure 1). Of these, 40 complete articles were reviewed, and 15 eligible articles were identified, describing 10 distinct studies and 1 extension study (Table 1). The time between baseline and follow-up assessments of symptoms varied from a minimum of 7–14 weeks in a cohort study [36] to a maximum of 24 months in another double-blind comparison of full and partial anemia correction in incident hemodialysis patients [37, 38]. The only placebo-controlled RCT by the Canadian Erythropoietin Study Group followed patients for 6 months [4, 12, 17]; other studies comparing high versus low Hb level or intravenous versus subcutaneous administration included either a 6-month or a 1-year assessment [30, 34, 35]; the rest of the single-arm cohort studies had shorter follow-up than 1 year [27–29, 31–33].

The one placebo-controlled RCT assessing fatigue used the KDQ and found a 22% increase in KDQ fatigue scale in the lower Hb treatment arm and a 26.2% increase in the higher Hb treatment arm compared to only a little change (2.3%) over 6 months in the placebo arm (Table 2) [12, 17]. These results were recently re-analyzed based on intention to treat and comparing the combined ESA-receiving groups to placebo with very similar results (0% change in placebo group versus 23.8% in ESA group) [4]. In addition, this study was extended in an open-label fashion to start or continue patients on erythropoietin for an additional 12 months, during which time the patients formerly assigned to placebo experienced an 18% improvement in fatigue and the patients already assigned to receive erythropoietin had no further change in fatigue [31].

Three RCTs, all of which were open label and did not include a placebo group, varied in the comparators, with different Hb levels and follow-up time (Table 2). One compared intravenous to subcutaneous ESA among ESA-naïve patients and found moderate to large improvements in fatigue [11.1%; effect size

Table 1. Summary of descriptive information and research methods for fatigue articles

<table>
<thead>
<tr>
<th>Author (year)</th>
<th>Study type</th>
<th>Treatment groups (V)</th>
<th>Pre-treatment Hb Mean (SD)</th>
<th>Treatment target</th>
<th>Instrument</th>
<th>Follow-up (months)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Keown[4] (2010)</td>
<td>RCT</td>
<td>Placebo (n = 40)</td>
<td>Hb 7.5 (1.0) g/dL, HCT ≤ 30%; actual mean not reported</td>
<td>NA</td>
<td>KDQ fatigue</td>
<td>6</td>
</tr>
<tr>
<td>Auerc (1992) [27]</td>
<td>Cohort</td>
<td>EPO (n = 22)</td>
<td>Hb 11.0 (1.2) g/dL</td>
<td>None stated (achieved HCT 30–36%)</td>
<td>POMS fatigue</td>
<td>4, &gt;9</td>
</tr>
<tr>
<td>Evans (1990) [28]</td>
<td>Cohort</td>
<td>EPO (n = 329)</td>
<td>Hb 7.7 (1.5) g/dL</td>
<td>Hb 10.5–12.5 g/dL</td>
<td>KDQ fatigue</td>
<td>6</td>
</tr>
<tr>
<td>Wolcott (1989) [29]</td>
<td>Cohort</td>
<td>EPO (n = 15)</td>
<td>HCT 22.8% (no SD reported)</td>
<td>None stated</td>
<td>FACIT-Fatigue</td>
<td>4, &gt;10</td>
</tr>
<tr>
<td>Muirhead (1992) [30]</td>
<td>RCT</td>
<td>Intravenous EPO (n = 38)</td>
<td>Hb 8.0 (1.4) g/dL</td>
<td>Hb 10.5–12.0 g/dL</td>
<td>KDQ fatigue</td>
<td>6</td>
</tr>
<tr>
<td>Muirhead[4] (extension of CESG study) (1992) [31]</td>
<td>Cohort</td>
<td>Group 1 (n = 16)</td>
<td>Hb 7.4 (1.1) g/dL</td>
<td>Hb 10.5–12.0 g/dL</td>
<td>KDQ fatigue</td>
<td>12</td>
</tr>
<tr>
<td>Levin[4] (1993) [32]</td>
<td>Cohort</td>
<td>Group 2 (n = 46)</td>
<td>Hb 11.0 (1.4) g/dL</td>
<td>Hb 10.5–12.0 g/dL</td>
<td>KDQ fatigue</td>
<td>12</td>
</tr>
<tr>
<td>Beusterien[9] (1996) [33]</td>
<td>Cohort</td>
<td>EPO (n = 484)</td>
<td>Mean not stated; 78% &lt; HCT 30%</td>
<td>HCT 25.5% (3.8)</td>
<td>SF-36 vitality</td>
<td>4</td>
</tr>
<tr>
<td>Foley (2000) [34]</td>
<td>RCT</td>
<td>EPO low (n = 73)</td>
<td>Hb 10.4 (0.1) g/dL</td>
<td>Hb 13–14 g/dL</td>
<td>KDQ fatigue</td>
<td>12</td>
</tr>
<tr>
<td>Furuland (2003) [35]</td>
<td>RCT</td>
<td>EPO subnormal (n = 200)</td>
<td>Hb 11.0 (0.9) g/dL</td>
<td>Hb 9.0–12.0 g/dL</td>
<td>KDQ-fatigue</td>
<td>12</td>
</tr>
<tr>
<td>Fukuhara (2008) [36]</td>
<td>Cohort</td>
<td>EPO normal (n = 216)</td>
<td>Hb 11.0 (1.1) g/dL</td>
<td>Hb 13.5–16.0 g/dL</td>
<td>SF-36 vitality</td>
<td>1.75–4</td>
</tr>
<tr>
<td>Parfrey[7] (2005) [37]</td>
<td>RCT</td>
<td>EPO low (n = 300)</td>
<td>Hb 11.0 (1.2) g/dL</td>
<td>Hb 9.5–11.5 g/dL</td>
<td>SF-36 vitality; FACIT-Fatigue</td>
<td>24</td>
</tr>
<tr>
<td>Foley[4] (2009) [38]</td>
<td>RCT</td>
<td>EPO low (n = 300)</td>
<td>Hb 11.0 (1.2) g/dL</td>
<td>Hb 13.5–14.5 g/dL</td>
<td>SF-36 vitality; 6, 9, 12, 14, 18, 21, 24</td>
<td></td>
</tr>
</tbody>
</table>

DAR, darbepoetin alfa; EPO, epoetin alfa; HCT, hematocrit; NA, Not applicable; rHuEpo, recombinant human erythropoietin.

Hb and HCT values are shown as reported in the publication. (To convert an estimate of Hb to HCT, multiply Hb by 3; to convert an estimate of HCT to Hb, divide HCT by 3.)

Follow-up months, during which time the patients formerly assigned to placebo experienced an 18% improvement in fatigue and the patients already assigned to receive erythropoietin had no further change in fatigue [31].
(ES) = 0.36 for subcutaneous and 18.6%; ES = 0.57 for intravenous [30]. Two studies compared high versus low Hb targets among patients already receiving ESA treatment [34, 35] with slight but non-significant (range −0.2 to −6.6%) deterioration in the low-target group and slight (3.4% at 48 weeks in one study [35] and 10.4% at 24 weeks and 6.0% at 48 weeks in another) improvement in the high-target group [34].

Five articles [32, 33, 36–38], two of which were based on the same RCT comparing high (13.5–14.5 g/dL) versus low (9.5–11.5 g/dL) Hb level [37, 38], used the SF-36 vitality score to assess fatigue or energy level (Table 3). Another two articles based on a phase IV, open-label multicenter study among ESA-naïve patients showed substantial improvements of 22.7% and 24.8% after achieving a hematocrit of 30% at ~4-month follow-up [32, 33]. However, the RCTs of comparisons of partial and complete correction of anemia among previously treated patients reported little difference, ranging from a difference of 7% in the full correction group to 0.9% in the partial group at 48 weeks (P = 0.004) [37, 38]. This difference became smaller at 96 weeks with 2.2% in the fully corrected group and 4.0% in the partially corrected group (P = 0.22) [37, 38]. The last study, a single-arm

<table>
<thead>
<tr>
<th>Table 2. ESA impact on KDQ fatigue scores‡</th>
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<tbody>
<tr>
<td>Study</td>
</tr>
<tr>
<td>CESG (1990) [12, 17]</td>
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<td></td>
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<tr>
<td></td>
</tr>
<tr>
<td>Muirhead (1992) [30]</td>
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<tr>
<td></td>
</tr>
<tr>
<td>Muirhead (1992b) [31]</td>
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<tr>
<td></td>
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<tr>
<td>Foley (2000) [34]</td>
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<td></td>
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<tr>
<td>Furuland (2003) [35]</td>
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<td></td>
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<tr>
<td>Keown (2010) [4]</td>
</tr>
<tr>
<td></td>
</tr>
</tbody>
</table>

‡ES, effect size; HCT, hematocrit; SE, standard error.

bHb and HCT values are shown as reported in the publication. (To convert an estimate of Hb to HCT, multiply Hb by 3; to convert an estimate of HCT to Hb, divide HCT by 3).

c% Change = (follow-up mean − baseline mean)/baseline mean (calculated based on the data reported in the paper).

dES = (m2 − m1)/SD1. ES values were computed wherever possible.

Table 3. ESA impact on SF-36 vitality scores‡

<table>
<thead>
<tr>
<th>Study</th>
<th>Treatment targetb</th>
<th>Baseline</th>
<th>Follow-up</th>
<th>% Changec (ES)d</th>
</tr>
</thead>
<tbody>
<tr>
<td>Leven (1993) [32]</td>
<td>None stated (achieved HCT 30%) (n = 324)</td>
<td>42.7</td>
<td>52.4</td>
<td>16 weeks; 22.7%</td>
</tr>
<tr>
<td>Beustereiner (1996) [33]</td>
<td>None stated (achieved HCT 30%) (n = 484)</td>
<td>39.1 (22.6)</td>
<td>48.8 (22.1)</td>
<td>14 weeks; 24.8% (ES = 0.43)</td>
</tr>
<tr>
<td>Fukuhara (2008) [36]</td>
<td>No Hb stated (switch study) (n = 487)</td>
<td>62.5 (20.2)</td>
<td>66.1</td>
<td>7–14 weeks; 6.0% (ES = 0.18)</td>
</tr>
<tr>
<td>Parfrey (2005) [37]</td>
<td>Hb 9.5–11.5 g/dL (n = 300)</td>
<td>57.9 (SE = 1.5)</td>
<td>54.2 (SE = 1.1)</td>
<td>96 weeks</td>
</tr>
<tr>
<td>Foley (2009) [38]</td>
<td>Hb 13.5–14.5 g/dL (n = 296)</td>
<td>53.9 (SE = 1.7)</td>
<td>57.9 (SE = 1.1)</td>
<td>96 weeks</td>
</tr>
<tr>
<td></td>
<td>Hb 9.5–11.5 g/dL (n = 300)</td>
<td>57.9 (SE = 1.5)</td>
<td>52.4 (SE = 1.5)</td>
<td>96 weeks</td>
</tr>
<tr>
<td></td>
<td>Hb 13.5–14.5 g/dL (n = 296)</td>
<td>53.9 (SE = 1.7)</td>
<td>55.3 (SE = 1.5)</td>
<td>96 weeks</td>
</tr>
</tbody>
</table>

‡ES, effect size; HCT, hematocrit; SE = standard error.

bHb and HCT values are shown as reported in the publication. (To convert an estimate of Hb to HCT, multiply Hb by 3; to convert an estimate of HCT to Hb, divide HCT by 3).

c% Change = (follow-up mean − baseline mean)/baseline mean (calculated based on the data reported in the paper).

dES = (m2 − m1)/SD1. ES values were computed wherever possible.

ePapers refer to different phases of the National Cooperative rHu Erythropoietin Study.

fData included in Parfrey (2005) and Foley (2009) come from the same study.
prospective cohort study, measured vitality before and after switching patients from epoetin alfa to darbepoetin alfa, resulting in an increase in mean Hb from 10.4 to 11.4 g/dL and a 6% improvement in vitality [36]. The investigators demonstrated that vitality increased significantly in those patients with an Hb increase of 1 g/dL and in those patients with Hb levels >10.0 g/dL at the 7- to 14-week follow-up visit.

Finally, other instruments were used in some studies, including the NHP energy scale in two single-arm prospective cohort studies [27, 28], the FACIT-Fatigue scale in one RCT comparing high versus low Hb value [37] and the POMS Fatigue scale in one single-arm prospective cohort study [29] (Table 4). Both studies using the NHP reported highly significant improvements in fatigue (P = 0.001 in the Evans study and P = 0.0001 at 3- to 5-month follow-up and P = 0.0039 at 6-month follow-up in Auer study). Parfrey et al. [37] reported no significant change in the FACIT-Fatigue score despite the observed improvements on the SF-36 vitality score. Wolcott et al. [29], in a small cohort study of hemodialysis patients, reported a significant improvement in the POMS Fatigue score (P = 0.007).

Figure 2 summarizes individual studies by baseline Hb levels, achieved Hb and the average percentage change in fatigue score by the study design, including placebo-controlled trials, controlled trials without a placebo group and uncontrolled trials. Overall, the increase in fatigue score was greater when baseline Hb level was lower. Table 5 summarizes treatment arms of the studies by categories based on baseline Hb levels and change in Hb and by study design and shows the percentage change in fatigue score for each treatment group. Studies with a baseline Hb of <10 g/dL, with partial correction to a minimum Hb ≥10 g/dL showed an average 34.6% improvement in fatigue (not weighted by sample size). Studies with a baseline Hb ≥10 g/dL with ≥1 g/dL increase in Hb showed an average 5.5% improvement in fatigue outcomes, while studies with <1 g/dL increase in Hb (either placebo group or control arms) showed an average decline of 0.7% in fatigue outcomes.

### Discussion

There were surprisingly few studies assessing the effect of treatment with ESAs on fatigue among patients with ESRD, particularly considering the evidence linking anemia with fatigue and the long history of use of ESAs to treat the anemia associated with ESRD. Although several RCTs were identified in our study, only one blinded placebo-controlled trial of moderate size (n = 118, divided across three arms) assessed the effects of erythropoietin on fatigue among erythropoietin-naive patients [12]. This study showed a 22–26% improvement in fatigue as measured by the KDQ fatigue score [12]. It is notable that this placebo-controlled trial was the only published RCT to compare the effects of erythropoietin on fatigue with the placebo among patients with ESRD. Because the analytical method in the original paper was not based on an intent-to-treat population, the conclusion of the improvement in fatigue, physical symptoms and exercise tolerance attributed to ESA treatment was not firmly supported by current US Food and Drug Administration standards. A recent publication of the re-analysis of these clinical trial data among the intent-to-treat population comparing the ESA and placebo groups also demonstrated statistically significant improvements in fatigue outcomes [4].

This initial RCT was followed by several cohort studies introducing erythropoietin to previously untreated patients and using a variety of instruments to measure fatigue, including the SF-36 vitality score, NHP and POMS [27–29, 32, 33]. These cohort studies uniformly confirmed a statistically significant reduction in fatigue after a substantial increase in Hb as a result of treatment with erythropoietin.

Subsequent to these early studies among previously ESA-naive patients, a series of RCTs comparing a high Hb target to a low Hb target among patients with ESRD previously treated with erythropoietin were conducted [34, 35, 37, 38]. In these studies, a high Hb target was typically approximate to the average Hb level among the general population, i.e. 13–14

### Table 4. ESA impact on NHP energy scale, the FACIT-Fatigue, and the POMS fatigue scale

<table>
<thead>
<tr>
<th>Study</th>
<th>Instrument used</th>
<th>Treatment targetb</th>
<th>Baseline</th>
<th>Follow-up</th>
<th>% Changec (ES)d</th>
</tr>
</thead>
<tbody>
<tr>
<td>Auer (1992) [27]</td>
<td>NHP</td>
<td>Achieved Hb 10.8 g/dL in 3–5 months (n = 22)</td>
<td>75.5</td>
<td>24.0</td>
<td>Follow-up at 12–20 weeks; 68.2%</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Achieved Hb 12.8 g/dL in 6 months (n = 12)</td>
<td></td>
<td>27.7</td>
<td>Follow-up at 26 weeks; 63.3%</td>
</tr>
<tr>
<td>Evans (1990) [28]</td>
<td>NHP</td>
<td>HCT 32–38% (n = 329)</td>
<td>50.4</td>
<td>24.2</td>
<td>Follow-up at 4–56 weeks; 52.0%</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Achieved HCT 36.1% in 3–4 months (n = 15)</td>
<td></td>
<td>23.4</td>
<td>Follow-up at 13–70 weeks; 53.6%</td>
</tr>
<tr>
<td>Wolcott (1989) [29]</td>
<td>POMS</td>
<td>Achieved HCT 36.1% in 3–4 months (n = 15)</td>
<td>11.7</td>
<td>7.4</td>
<td>Follow-up at 12–16 weeks; 36.8%</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Achieved HCT 34.0% in 10 to 15 months (n = 15)</td>
<td></td>
<td>5.0</td>
<td>Follow-up at 40–60 weeks; 57.3%</td>
</tr>
<tr>
<td>Parfrey (2005) [37]</td>
<td>FACIT-Fatigue</td>
<td>Hb 9.5–11.5 g/dL (n = 300)</td>
<td>Not reported</td>
<td>68.1 (SE = 1.0)e</td>
<td>Follow-up at 48 weeks</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Hb 13.5–14.5 g/dL (n = 296)</td>
<td>Not reported</td>
<td>70.0 (SE = 1.0)</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>Hb 9.5–11.5 g/dL (n = 300)</td>
<td></td>
<td>64.8 (SE = 1.4)</td>
<td>Follow-up at 96 weeks</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Hb 13.5–14.5 g/dL (n = 296)</td>
<td></td>
<td>68.1 (SE = 1.5)</td>
<td></td>
</tr>
</tbody>
</table>

aES, effect size; HCT, hematocrit; SE, standard error.

bHb and HCT values are shown as reported in the publication. (To convert an estimate of Hb to HCT, multiply Hb by 3; to convert an estimate of HCT to Hb, divide HCT by 3).

c% Change = (follow-up mean - baseline mean)/baseline mean (calculated based on the data reported in the paper).

dES = (m2 - m1)/SD1. ES values were computed wherever possible.

eSEs were included in the table wherever the data were reported in the paper.
Fig. 2. Baseline Hb, achieved Hb and mean percentage PRO improvement by study design. Studies were grouped into three blocks based on the study design, including placebo-controlled trials, non-placebo-controlled trials and non-controlled trials. The left Y-axis shows the percentage fatigue improvement and the right Y-axis shows the Hb value. All the arms with available data in the baseline Hb level, the achieved Hb level and percentage improvement in fatigue score are depicted, using a diamond to represent baseline Hb level, a square to represent achieved Hb level and a histogram to represent percentage fatigue score improvement.

Table 5. Relationship between baseline Hb, Hb change and PRO change

<table>
<thead>
<tr>
<th>Hemoglobin relationship and Study design</th>
<th>Study</th>
<th>Treatment group</th>
<th>Baseline Hb</th>
<th>Achieved Hb</th>
<th>% PRO change</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hb baseline ≤ 10 g/dL treated to Hb ≥ 10 g/dL (≥ 1 g/dL change)</td>
<td>Placebo-controlled CESG [12]</td>
<td>Hb 9.5–11 g/dL</td>
<td>6.9</td>
<td>10.2</td>
<td>22.0</td>
</tr>
<tr>
<td>Placebo-controlled CESG [12]</td>
<td>Hb 11.5–13 g/dL</td>
<td>7.1</td>
<td>11.7</td>
<td>26.2</td>
<td></td>
</tr>
<tr>
<td>Controlled Muirhead-extension [31]</td>
<td>Extension; ex placebo</td>
<td>7.4</td>
<td>11.2</td>
<td>18.6</td>
<td></td>
</tr>
<tr>
<td>Controlled Muirhead [30]</td>
<td>Subcutaneous</td>
<td>8.0</td>
<td>10.9</td>
<td>11.1</td>
<td></td>
</tr>
<tr>
<td>Uncontrolled Auer [27]</td>
<td>Intravenous</td>
<td>7.7</td>
<td>11.2</td>
<td>18.0</td>
<td></td>
</tr>
<tr>
<td>Uncontrolled Auer [27]</td>
<td>4 months</td>
<td>7.5</td>
<td>10.8</td>
<td>68.2</td>
<td></td>
</tr>
<tr>
<td>Uncontrolled Wolcott [29]</td>
<td>&gt; 6 months</td>
<td>7.5</td>
<td>12.8</td>
<td>63.3</td>
<td></td>
</tr>
<tr>
<td>Uncontrolled Wolcott [29]</td>
<td>3–4 months</td>
<td>7.6</td>
<td>12.0</td>
<td>36.8</td>
<td></td>
</tr>
<tr>
<td>Uncontrolled Wolcott [29]</td>
<td>10–15 months</td>
<td>7.6</td>
<td>11.3</td>
<td>57.3</td>
<td></td>
</tr>
<tr>
<td>Uncontrolled Beusterien [33]</td>
<td>Treatment</td>
<td>8.5</td>
<td>10.0</td>
<td>24.8</td>
<td></td>
</tr>
<tr>
<td>Controlled Foley [34]</td>
<td>Normal Hb</td>
<td>12.2</td>
<td>14.0</td>
<td>6.0</td>
<td></td>
</tr>
<tr>
<td>Hb baseline ≥ 10 g/dL treated (≥ 1 g/dL change)</td>
<td>Controlled Parfrey [37]</td>
<td>Hb 13.5–14.5 g/dL</td>
<td>11.0</td>
<td>13.3</td>
<td>7.0</td>
</tr>
<tr>
<td>Controlled Furuland [35]</td>
<td>Normal Hb</td>
<td>11.0</td>
<td>13.5</td>
<td>3.4</td>
<td></td>
</tr>
<tr>
<td>Placebo-controlled CESG [12]</td>
<td>Placebo</td>
<td>7.1</td>
<td>7.4</td>
<td>2.3</td>
<td></td>
</tr>
<tr>
<td>Controlled CESG-Extension [31]</td>
<td>Extension; ex treatment</td>
<td>10.9</td>
<td>11.6</td>
<td>0.0</td>
<td></td>
</tr>
<tr>
<td>Controlled Furuland [35]</td>
<td>Subnormal Hb</td>
<td>11.0</td>
<td>11.0</td>
<td>−6.6</td>
<td></td>
</tr>
<tr>
<td>Controlled Foley [34]</td>
<td>Subnormal Hb</td>
<td>10.4</td>
<td>10.4</td>
<td>0.2</td>
<td></td>
</tr>
<tr>
<td>Controlled Parfrey [37]</td>
<td>Hb 9.5–11.5 g/dL</td>
<td>11.0</td>
<td>11.0</td>
<td>0.9</td>
<td></td>
</tr>
</tbody>
</table>

*aHb, Hemoglobin.*
pared with the group targeting at a lower Hb level [34, 35, 37, 38]. Our results seem consistent with a recent meta-analysis on the impact of high versus low Hb level on HRQOL for CKD patients and with a recent systematic review of the effects of ESAs on fatigue and physical function. In the meta-analysis, researchers included RCTs that measured HRQOL improvement associated with anemia treated by ESA and suggested that targeting Hb in excess of 12 g/dL leads to small and not clinically meaningful improvements in HRQOL compared with partial correction of anemia [39]. In the systematic review, treatment with ESAs was associated with consistent improvement in energy, but the association between target Hb and degree of improvement was more difficult to determine.

Our study has several limitations. We originally intended to perform a meta-analysis of the effects of ESAs on fatigue among patients with ESRD but discovered that differences in patient characteristics (particularly differences in pre-study Hb levels related to prior ESA treatment), use of different fatigue instruments, different durations of ESA therapy and, in many cases, poor quality studies that did not report the magnitude or variability of the effect of ESA on fatigue, precluded meta-analysis. Thus, we performed a qualitative rather than a quantitative synthesis of the evidence on the effects of ESAs on fatigue. It should be noted that we calculated the percentage change in fatigue scores across different instruments, which allowed us to estimate the relationship of change in fatigue to the baseline Hb level and change in Hb level. The interpretation of such comparisons should be made with caution as fatigue scores based on different instruments entail different scales and algorithms. Although we have drawn some conclusions from the available evidence, we believe that the available evidence is not sufficiently robust to allow a clear recommendation of the optimal target Hb from the standpoint of management of the anemia-associated symptom of fatigue. However, it is notable that we did not uncover any data that would strongly support a target different from the clinically acceptable range of 10–12 g/dL.

Conclusions

Placebo-controlled RCT data and several cohort studies demonstrate that partial correction of anemia with ESAs results in improvement in symptoms of fatigue compared to no treatment or in the cohort studies of pre- and post-ESA use. No considerable improvements in fatigue were observed in studies comparing high versus low Hb level among dialysis patients. However, additional data would be helpful in order to more fully delineate the optimal Hb target of ESA therapy to maximize improvement in other HRQOL outcomes in addition to fatigue while minimizing any potential harmful effects.

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