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Martí-Carvajal AJ, Agreda-Pérez LH, Solà I

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[Intervention Review]

Erythropoiesis-stimulating agents for anemia in rheumatoid arthritis

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ABSTRACT

Background

Rheumatoid arthritis (RA) is a chronic and systemic inflammatory disorder that mainly affects the small joints of the hands and feet. Erythropoiesis-stimulating agents have been used to treat anemia, one of the extra-articular manifestations of RA. Although anemia is less of a problem now because of the reduction in inflammation due to disease-modifying antirheumatic drugs (DMARDs), it could still be an issue in countries where DMARDs are not yet accessible.

Objectives

We assessed the clinical benefits and harms of erythropoiesis-stimulating agents for anemia in rheumatoid arthritis.

Search methods

We searched the Cochrane Central Register of Controlled Trials (CENTRAL) in *The Cochrane Library* (issue 7 2012), Ovid MEDLINE and Ovid MEDLINE(R) In-Process & Other Non-Indexed Citations (1948 to 7 August 2012), OVID EMBASE (1980 to 7 August 2012), LILACS (1982 to 7 August 2012), the Clinical Trials Search Portal of the World Health Organization, reference lists of the retrieved publications and review articles. We did not apply any language restrictions.

Selection criteria

We included randomized controlled trials (RCTs) in patients aged 16 years or over, with a diagnosis of rheumatoid arthritis affected by anemia. We considered health-related quality of life, fatigue and safety as the primary outcomes.

Data collection and analysis

Two authors independently performed trial selection, risk of bias assessment, and data extraction. We estimated difference in means with 95% confidence intervals (CIs) for continuous outcomes. We estimated risk ratios with 95% CIs for binary outcomes.

Main results

We included three RCTs with a total of 133 participants. All trials compared human recombinant erythropoietin (EPO), for different durations (8, 12 and 52 weeks), versus placebo. All RCTs assessed health-related quality of life. All trials had high or unclear risk of bias for most domains, and were sponsored by the pharmaceutical industry. Two trials administered EPO by a subcutaneous route while the other used an intravenous route.

We decided not to pool results from trials, due to inconsistencies in the reporting of results.

Health-related quality of life: subcutaneous EPO – one trial with 70 patients at 52 weeks showed a statistically significant difference in improvement of patient global assessment (median and interquartile range 3.5 (1.0 to 6.0) compared with placebo 4.5 (2.0 to 7.5) (P = 0.027) on a VAS scale (0 to 10)). The other shorter term trials (12 weeks with subcutaneous EPO and eight weeks with intravenous administration) did not find statistically significant differences between treatment and control groups in health-related quality of life outcomes.

Change in hemoglobin: both trials of subcutaneous EPO showed a statistically significant difference in increasing hemoglobin levels; (i) at 52 weeks (one trial, 70 patients), intervention hemoglobin level (median 134, interquartile range 110 to 158 g/litre) compared with the placebo group level (median 112, interquartile range; 86 to 128 g/litre) (P = 0.0001); (ii) at 12 weeks (one trial, 24 patients) compared with placebo (difference in means 8.00, 95% CI 7.43 to 8.57). Intravenous EPO at eight weeks showed no statistically significant difference in increasing hematocrit level for EPO versus placebo (difference in means 4.69, 95% CI -0.17 to 9.55; P = 0.06).

Information on withdrawals due to adverse events was not reported in two trials, and one trial found no serious adverse events leading to withdrawals. None of the trials reported withdrawals due to high blood pressure, or to lack of efficacy or to fatigue.

Authors' conclusions

We found conflicting evidence for erythropoiesis-stimulating agents to increase quality of life and hemoglobin level by treating anemia in patients with rheumatoid arthritis. However, this conclusion is based on randomized controlled trials with a high risk of bias, and relies on trials assessing human recombinant erythropoietin (EPO). The safety profile of EPO is unclear. Future trials assessing erythropoiesis-stimulating agents for anemia in rheumatoid arthritis should be conducted by independent researchers and reported according to the CONSORT statements. Trials should be based on Outcome Measures in Rheumatoid Arthritis Clinical Trials (OMERACT) and The Patient-Centered Outcomes Research Institute (PCORI) approaches for combining both clinician and patient perspectives.

PLAIN LANGUAGE SUMMARY

Erythropoiesis-stimulating agents for anemia in rheumatoid arthritis

Researchers in the Cochrane Collaboration conducted a review of the effect of erythropoiesis-stimulating agents for anemia in patients with rheumatoid arthritis. After searching for all relevant studies, they found three studies covering 133 people. Their findings are summarised below:

The review shows that in people with anemia and rheumatoid arthritis:

- it is uncertain whether erythropoiesis-stimulating agents improve quality of life or hemoglobin levels.
- it is unknown whether erythropoiesis-stimulating agents improve fatigue, as this was not measured by the studies.

We do not have precise information about side effects and complications. This is particularly true for rare but serious side effects, which may include thromboembolic complications.

What is anemia in rheumatoid arthritis and what are erythropoiesis-stimulating agents?

When you have rheumatoid arthritis, your immune system, which normally fights infection, attacks the lining of your joints. This makes them swollen, stiff and painful. The small joints of the hands and feet are usually affected first. As the disease progresses, other complications may appear, including anemia (low hemoglobin level). Hemoglobin is a protein in red blood cells that carries oxygen. Anemia is a condition in which the body does not have enough healthy red blood cells. Erythropoietin is a hormone produced in the kidney, which increases the production of red blood cells. Erythropoiesis-stimulating agents work to increase red blood cell production.

Summary of findings for the main comparison. Erythropoietin (subcutaneous or intravenous at varying dosages) compared to placebo for anemia in patients with rheumatoid arthritis

Erythropoietin (subcutaneous or intravenous at varying dosages) compared to placebo for anemia in patients with rheumatoid arthritis

Patient or population: anemia in patients with rheumatoid arthritis
Settings: outpatient
Intervention: erythropoietin (subcutaneous or intravenous at varying dosages)
Comparison: placebo

Outcomes	Illustrative comparative risks* (95% CI)		Relative effect (95% CI)	No of Participants (studies)	Quality of the evidence (GRADE)	Comments
	Assumed risk	Corresponding risk				
	Placebo	Erythropoietin (subcutaneous or intravenous at varying dosages)				
Health-related quality of life Follow-up: 8 to 52 weeks	See comment	See comment		136 (3 studies[1])	⊕⊖⊖⊖ **very low** [2,3]	Peeters 1996, with 70 participants followed up during 52 weeks reporting patients' global assessment (VAS score 0 to 10), found statistically significant differences comparing EPO versus placebo (median and interquartile range at 52 weeks: 3.5 (1.0 to 6.0) and 4.5 (2.0 to 7.5) P = 0.027, respectively. Pincus 1990, with 17 participants followed up during 8 weeks, reported no significant differences between groups of patient satisfaction in activities of daily living using the mHAQ[5] but data were not provided. Nordström 1997, with 46 participants followed up at 12 weeks, reported no significant difference between groups in Stanford Health Assessment Questionnaire scores, Nottingham Health Profile scores, classification of functional class or joint score index scores.
Hemoglobin (Hb) level at		See comment		116 (2 studies[4])	⊕⊕⊖⊖ **low** [2]	Nordström 1997 (46 participants) reported a statistically significant increase in hemoglobin level at 12 weeks in

the end of the study Follow-up: 12 to 52 weeks[4]						the EPO group compared with placebo group (MD 8.00, 95% CI 7.43 to 8.57 g/l; P = 0.00001) Peeters 1996 (70 participants) reported a statistically significant increase in hemoglobin level at 52 weeks in the EPO group (median 134; interquartile range 110 to 158 g/L) compared with placebo group (median 112; interquartile range 86 to 128 g/L) (P = 0.001).
Fatigue Not reported	See comment	See comment	Not estimable	-	See comment	This outcome was not assessed by any of the trials.
Safety (Adverse events including adverse drug reaction) Follow-up: 8 to 52 weeks	See comment	See comment	Not estimable	(3 studies[1])	⊕⊝⊝⊝ **very low** [2,3]	Nordström 1997 found no significant alterations in pulse, blood pressure, platelet counts, albumin, creatinine, alanine aminotransferase, or aspartate aminotransferase values . Peeters 1996 assessed adverse events and found no significant rise in blood pressure and thromboembolic complications. Pincus 1990 found no adverse reactions.
Withdrawals due to adverse events	See comment	See comment	Not estimable	-	See comment	Nordström 1997 reported no serious adverse events causing premature discontinuation. This outcome was not reported by the other two trials (Peeters 1996; Pincus 1990).
Withdrawals due to lack of efficacy	See comment	See comment	Not estimable	-	See comment	This outcome was not assessed by any of the trials.
Withdrawals due to high blood pressure	See comment	See comment	Not estimable	-	See comment	This outcome was not assessed by any of the trials.

*The basis for the **assumed risk** (e.g. the median control group risk across studies) is provided in footnotes. The **corresponding risk** (and its 95% confidence interval) is based on the assumed risk in the comparison group and the **relative effect** of the intervention (and its 95% CI).
CI: Confidence interval; **RR:** Risk ratio;

GRADE Working Group grades of evidence
High quality: Further research is very unlikely to change our confidence in the estimate of effect.
Moderate quality: Further research is likely to have an important impact on our confidence in the estimate of effect and may change the estimate.
Low quality: Further research is very likely to have an important impact on our confidence in the estimate of effect and is likely to change the estimate.
Very low quality: We are very uncertain about the estimate.

1. Nordström 1997, Peeters 1996, Pincus 1990
2. Almost all domains had a high or unclear risk of bias.
3. Small sample size
4. Nordström 1997, Peeters 1996
5. mHAQ: modified Stanford Health Assessment Questionnaire

BACKGROUND

Description of the condition

The burden of anemia in rheumatoid arthritis

Rheumatoid arthritis is a chronic and systemic inflammatory disorder that mainly affects the small joints of the hands and feet (Lee 2001). The criteria for the classification of rheumatoid arthritis are described in Arnett 1988 (Appendix 1). Recently, the immunopathogenesis of rheumatoid arthritis has been described (Imboden 2009; McInnes 2011). Rheumatoid arthritis has variable extra-articular manifestations which are known as comorbidities (Grassi 1998; Hochberg 2008; Michaud 2007; Turesson 2003; Young 2007). Anemia is one of those comorbidities (Appendix 2), and this has a prevalence ranging from 33% to 60% (Al-Ghamdi 2009; Furst 2009; Wilson 2004). According to the World Health Organization, hemoglobin thresholds used to define anemia are 120 g/L for non-pregnant women (≥15 years old) and 130 g/L for men (≥15 years old) (WHO 2008). However, anemia is less of a problem now because of the reduction in inflammation due to disease-modifying antirheumatic drugs (DMARDs) (Blumenauer 2002; Blumenauer 2003; Maxwell 2009; Mertens 2009; Navarro-Sarabia 2005; Ruiz Garcia 2011; Singh 2009; Singh 2010a; Singh 2010b; Singh 2011), but it can still be an issue in countries where the drugs are not yet accessible.

Why do patients with rheumatoid arthritis have anemia?

Rheumatoid arthritis is a chronic inflammatory state characterized by high circulating levels of interleukin-6 (IL-6) (Cronstein 2007; Dayer 2010; Fonseca 2009; Kishimoto 2006; Nicolaisen 2008). IL-6 stimulates the hepatic production of hepcidin (Dayer 2010; Ganz 2009; Raj 2009; Zhang 2009), which is the main iron regulatory hormone (Andrews 2007; Andrews 2008; Lee 2009; Muñoz 2009; Nemeth 2003; Sasu 2010). This hormone causes inhibition of iron release from macrophages which generates iron sequestration (Ganz 2009; Nemeth 2004). It reduces the iron supply to erythropoiesis-generating anemia called 'anemia of inflammation', which shows the interplay between iron and immune function (Demirag 2009; Ganz 2009; Jayaranee 2009; Roy 2005; Weiss 2009). This anemia is also known as 'anemia of chronic disease' (Agarwal 2009; Cartwright 1966; Means 1995; Theurl 2009; Masson 2011). The term 'anemia of inflammation' reflects its pathophysiology (Ganz 2009).

Other factors for explaining the pathogenesis of anemia in rheumatoid arthritis

Anemia in rheumatoid arthritis due to serum immunoreactive erythropoietin has been described (Hochberg 1988), and lower levels of serum erythropoietin in these patients may contribute to the pathogenesis of anemia (Baer 1997). Furthermore, tumour necrosis factor alpha, interleukin-1 (IL-1), and interferon-gamma (IFN-gamma) are factors mediating impaired erythropoiesis in anemia of chronic disease in active rheumatoid arthritis (Capocasale 2008; Moreland 2009; Papadaki 2002; Smith 1992; Vreugdenhil 1992a; Zhu 2000). Patients with rheumatoid arthritis and suffering with anemia have a decreased sensitivity of bone marrow erythroblasts to interleukin-3, which has hematopoietic growth-promoting activity (Jaworski 2008; Wu 2003). In summary, the pathophysiology of anemia in rheumatoid arthritis involves three mechanisms: disturbances of iron homeostasis, inhibition of erythroid progenitor of proliferation and differentiation, and blunted erythropoietin response (Weiss 2002).

Description of the intervention

Erythropoietin is a glycoprotein hormone that is produced in the kidney and acts through specific receptors on hematopoietic precursor cells to increase the production of red blood cells (Glaspy 2009).

Erythropoiesis-Stimulating Agents (ESAs)

There are two types of erythropoiesis-stimulating agents: recombinant human erythropoietin (alpha and beta) and darbepoetin alpha. Recombinant human erythropoietin is a hemopoietic growth factor that acts as a primary regulator of erythropoiesis. It is used for the treatment of chronic anemia associated with rheumatoid arthritis (Coussons 2005). Darbepoetin alpha is an analogue of recombinant human erythropoietin. Both agents share the same mechanism of action, but darbepoetin alpha has a three-fold longer terminal half-life (25.3 hours), after intravenous administration, than recombinant human erythropoietin (8.5 hours) (Cases 2003; Ibbotson 2001).

Why it is important to do this review

There are randomized controlled trials (Murphy 1994; Nordström 1997; Peeters 1996; Pincus 1990), clinical trials (Arndt 2005; Fantini 1992; Gudbjörnsson 1992; Kaltwasser 2001; Kato 1994; Pettersson 1993; Pettersson 1994; Salvarani 1991; Swaak 1994; Takashina 1990; Tauchi 1990; Vreugdenhil 1992b) and case reports (Krantz 1990; Means 1989) using human recombinant erythropoietin for treating anemia in rheumatoid arthritis. However, this drug was not approved for this indication.

This systematic review is important for the following issues.
1. Anemia is a comorbidity with negative impact on quality of life in patients with rheumatoid arthritis (Han 2007; Michaud 2007). Low hemoglobin levels may be associated with rheumatoid arthritis disease severity and the presence of certain comorbidities (Furst 2009).
2. Anemia is associated with the severity of rheumatoid arthritis, and its successful treatment leads to a significant improvement in the quality of life scores in patients with rheumatoid arthritis (Wilson 2004).
3. The clinical effectiveness of erythropoiesis-stimulating agents could be affected (hyporesponsiveness to erythropoietic therapy) by chronic inflammation (Macdougall 2005; van der Putten 2008).
4. Erythropoiesis-stimulating agents have been associated with an increased risk of mortality and cardiovascular events in cancer patients (Bennet 2008; Hershman 2009), and in patients with chronic kidney disease (Unger 2010). Both erythropoiesis-stimulating agents have been labelled with a warning by the Food and Drug Administration due to the following adverse events: increased mortality, serious cardiovascular and thromboembolic events, and increased risk of tumor progression or recurrence (FDA 2008a; FDA 2008b).

A systematic review, with rigorous assessment of the risk of bias, of the most up-to-date evidence will help clinicians make informed decisions about the use of erythropoiesis-stimulating agents for treating anemia in patients with rheumatoid arthritis.

OBJECTIVES

To assess the clinical benefits and harms of erythropoiesis-stimulating agents for anemia in rheumatoid arthritis.

METHODS

Criteria for considering studies for this review

Types of studies

We included randomized controlled trials irrespective of their publication status, language and country of origin. We included trials irrespective of their follow-up duration.

Types of participants

We included patients aged 16 years and older, with a diagnosis of rheumatoid arthritis and affected by anemia.

1. Diagnosis of rheumatoid arthritis was based on the American College of Rheumatology criteria (ACR) (Arnett 1988). See Appendix 1
2. Diagnosis of anemia was based on the World Health Organization (WHO) criteria. See Appendix 2.

Types of interventions

Intervention

Erythropoiesis-stimulating agents (epoetin (alpha or beta) or darbepoetin alpha) alone or in combination with oral or parenteral iron supplementation.

Control

1. Epoetin alpha compared with epoetin beta.
2. Darbepoetin alpha versus epoetin (alpha or beta).
3. Epoetin alpha or beta versus placebo or no medication.
4. Darbepoetin alpha versus placebo or no medication.
5. Any of the erythropoiesis-stimulating agents versus standard treatment of anemia (Hematinics - iron, folic acid, packed red cell blood transfusion, or both).
6. Any of the erythropoiesis-stimulating agents plus iron, folic acid, or both, versus placebo or versus standard treatment of anemia.

We accepted as potentially eligible any trials that assessed any erythropoiesis-stimulating agents regimen, in terms of route of administration (intravenous or subcutaneous), dosage, or treatment duration. We included trials that used hematinics as co-interventions, administered by any route, dosage or treatment duration.

Types of outcome measures

Primary outcomes

1. Health-related quality of life: “the degree to which persons perceive themselves able to function physically, emotionally, mentally, and socially” (Porta 2008). To be included in the review, trials had to use standardized scales (e.g. European League Against Rheumatism (EULAR), Disease Activity Score (DAS28), Health Assessment Questionnaire Disability Index (HAQ-DI), Routine Assessment of Patient Index Data 3 (RAPID3), Clinical Disease Activity Index (CDAI)).
2. Fatigue (Kirwan 2007).
3. Safety:

- *Adverse events*: "any untoward medical occurrence that may present during treatment with a pharmaceutical product but which does not necessarily have a causal relationship with this treatment" (Nebeker 2004);
- *Adverse drug reaction*: "a response to a drug which is noxious and uninitiated and which occurs at doses normally used in man for prophylaxis, diagnosis, or therapy of disease, or for the modification of physiologic functions" (Nebeker 2004). (e.g. high blood pressure).

Secondary outcomes

1. Hemoglobin (Hb) level at the end of the study.
2. Withdrawals due to adverse events.
3. Withdrawals due to lack of efficacy.
4. Withdrawals due to high blood pressure.
5. Withdrawals due to high disease activity.
6. Withdrawals due to poor compliance.

Search methods for identification of studies

Electronic searches

We searched the Cochrane Central Register of Controlled Trials (CENTRAL) in *The Cochrane Library* (issue 7, 2012), Ovid MEDLINE and Ovid MEDLINE(R) In-Process & Other Non-Indexed Citations (1948 to 7 August 2012), OVID EMBASE (1980 to 17 August 2012), and LILACS (1982 to 7 August 2012). See Appendix 3; Appendix 4; Appendix 5; Appendix 6; Appendix 7; Appendix 8 for full search strategies.

Searching other resources

We searched the Clinical Trials Search Portal of the World Health Organization (http://apps.who.int/trialsearch/) to identify ongoing and unpublished trials.

We also searched the reference lists of the retrieved publications and review articles. We did not apply any language restrictions.

Date of the most recent search: 7 August 2012.

Data collection and analysis

Selection of studies

AMC and DS screened the search results for potentially relevant trials, and assessed them independently. They resolved disagreements through discussion with LAP and IS to reach a consensus.

Data extraction and management

AMC and DS extracted the data using the agreed form, and resolved discrepancies through discussion. IS checked the data entered into Review Manager 5 (RevMan 2011) for accuracy.

Assessment of risk of bias in included studies

All review authors independently assessed the risk of bias for each included trial, using the domain-based evaluation as described in the *Cochrane Handbook for Systematic Reviews of Interventions* (Higgins 2011). All review authors checked the assessments, discussed discrepancies and achieved consensus.

The definition of each domain classification is given below:

Generation of allocation sequence (checking for possible selection bias)

- Low risk of bias, if the allocation sequence was generated by a computer or random number table, drawing of lots, tossing of a coin, shuffling of cards, or throwing dice.
- Unclear risk of bias, if the trial was described as randomized but the method used for the allocation sequence generation was not described.
- High risk of bias, if a system involving dates, names, or admittance numbers was used for the allocation of patients. These studies are known as quasi-randomized and were excluded from the present review when assessing beneficial effects.

Allocation concealment (checking for possible selection bias)

- Low risk of bias, if the allocation of patients involved a central independent unit, on-site locked computer, identical-appearing numbered drug bottles or containers prepared by an independent pharmacist or investigator, or sealed envelopes.
- Unclear risk of bias, if the trial was described as randomized but the method used to conceal the allocation was not described.
- High risk of bias, if the allocation sequence was known to the investigators who assigned participants or if the study was quasi-randomized. The latter was excluded from the present review when assessing beneficial effects.

Blinding or masking (checking for possible performance or detection bias)

We assessed the adequacy of blinding separately for participants, carers/personnel and outcome assessors.

- Low risk of bias: participants, carers/personnel and/or outcome assessors blinded from knowledge of which intervention the participant received, or the lack of blinding could not have affected the results;
- High risk of bias: participants, carers/personnel and/or outcome assessors were not blinded from the knowledge of which intervention the participant received and this could have affected the results;
- Unclear risk of bias: the blinding of participants, carers/personnel and outcome assessors was not reported.

Incomplete outcome data (checking for possible attrition bias through withdrawals, dropouts, protocol deviations)

- Low risk of bias (any one of the following): No missing outcome data; reasons for missing outcome data unlikely to be related to true outcome (for survival data, censoring unlikely to be introducing bias); missing outcome data balanced in numbers across intervention groups, with similar reasons for missing data across groups; for dichotomous outcome data, the proportion of missing outcomes compared with observed event risk not enough to have a clinically relevant impact on the intervention effect estimate; for continuous outcome data, plausible effect size (difference in means or standardized difference in means) among missing outcomes not enough to have a clinically relevant impact on observed effect size; missing data have been imputed using appropriate methods.
- High risk of bias (any one of the following): reason for missing outcome data likely to be related to true outcome, with either imbalance in numbers or reasons for missing data across intervention groups; for dichotomous outcome data, the proportion of missing outcomes compared with observed event risk enough to induce clinically relevant bias in intervention effect estimate; for continuous outcome data, plausible effect size (difference in means or standardized difference in means) among missing outcomes enough to induce clinically relevant bias in observed effect size; 'As-treated' analysis done with substantial departure of the intervention received from that assigned at randomizations; potentially inappropriate application of simple imputation.
- Unclear risk of bias (any one of the following): insufficient reporting of attrition/exclusions to permit judgement of 'low risk' or 'high risk' (e.g. number randomized not stated, no reasons for missing data provided); the study did not address this outcome.

Selective reporting bias (Outcome reporting bias)

- Low risk of bias (any one of the following): the study protocol is available and all the pre-specified (primary and secondary) outcomes were reported in the final report, or the study protocol was not available but it was clear that the published reports included all expected outcomes.
- High risk of bias (any one of the following): not all of the study's pre-specified primary outcomes have been reported; one or more primary outcomes is reported using measurements, analysis methods or subsets of the data (e.g. subscales) that were not pre-specified; one or more reported primary outcomes were not prespecified (unless clear justification for their reporting is provided, such as an unexpected adverse effect); one or more outcomes of interest in the review are reported incompletely so that they cannot be entered in a meta-analysis; the study report fails to include results for a key outcome that would be expected to have been reported for such a study.
- Unclear risk of bias insufficient information available to permit judgement of 'Low risk' or 'High risk'.

Other bias

- Low risk of bias, the trial appeared to be free of other components that could put it at risk of bias.
- Unclear risk of bias, the trial may or may not be free of other components that could put it at risk of bias.
- High risk of bias, there were other factors in the trial that could put it at risk of bias.

AMC entered the data into RevMan 5, and DS and IS checked them.

Measures of treatment effect

If we had conducted meta-analyses, we would have used the following procedures (and will apply these for future updates, if possible):

Both health-related quality of life and fatigue data would be analysed as continuous variables. We would present results as summary standardized mean differences (SMDs) with 95% confidence intervals (CIs).

For dichotomous data (safety and withdrawals), we would present results as summary risk ratios (RRs) with 95% CIs.

For hemoglobin levels, we have presented results as difference of means (MD) with 95% CIs.

Dealing with missing data

We would have used the following procedures (and will apply these for future updates, if possible):

We would have noted levels of attrition and explored the impact of high levels of missing data in the overall assessment of treatment effect by using sensitivity analyses.

For all outcomes we would have carried out analysis, as far as possible, on an intention-to-treat basis (i.e. we would have attempted to include all participants randomized to each group in the analyses). If intention-to-treat analysis had not been carried out, then we would have attempted a per-protocol or complete case analysis. The denominator for each outcome in each trial would have been the number randomized minus any participants whose outcomes are known to be missing.

Assessment of heterogeneity

We would have used the following procedures (and will apply these for future updates, if possible). We would have used the I^2 statistic to measure statistical heterogeneity between the trials in each analysis. This describes the percentage of total variation across trials that is due to heterogeneity rather than to sampling error (Higgins 2003). We would have considered there to be substantial statistical heterogeneity if the I^2 was greater than 50% (Higgins 2011), and would have explored this by prespecified subgroup analysis.

Assessment of reporting biases

We would have used the following procedures (and will apply these for future updates, if possible). When we suspected reporting bias (see 'Selective reporting bias' above), we would have attempted to contact study authors to obtain missing outcome data. When this was not possible, and if the missing data were thought to introduce serious bias, we would have used sensitivity analyses to explore the impact of including such studies in the overall assessment of results.

We would also have attempted to assess whether the review is subject to publication bias, by using a funnel plot to graphically illustrate variability between trials. If asymmetry were detected, we would have explored causes other than publication bias (e.g. selective outcome reporting, poor methodological quality in smaller studies, true heterogeneity) (Higgins 2011). In future updates we will construct a funnel plot, provided we have 10 or more randomized controlled trials (Sterne 2011).

Data synthesis

We would have used the procedures previously described (and will apply these for future updates, if possible). We would have carried out statistical analysis using the RevMan 5 software (RevMan 2011) and summarized the findings using a random-effects model, as differences would have been anticipated in terms of interventions and patients. When I^2 is greater than 50%, suggesting substantial heterogeneity, we may decide not to conduct meta-analysis.

Subgroup analysis and investigation of heterogeneity

We would have used the following procedures (and will apply these for future updates, if possible). We anticipated clinical heterogeneity for the following participant and intervention characteristics, and therefore we would have carried out the following subgroup analyses:

1. type of intervention (EPO versus darbepoetin)
2. duration of administration
3. gender
4. erythropoiesis-stimulating agents with and without hematinics
5. year of publication.

We would have restricted subgroup analysis to primary outcomes only (Higgins 2011).

Sensitivity analysis

We would have used the following procedures (and will apply these for future updates, if possible). If sufficient trials are identified, we plan to conduct a sensitivity analysis comparing the results using all the included trials. We would have compared trials with high methodological quality (studies classified as having a 'low risk of bias') versus those of lower methodological quality (classified as having an 'unclear' or 'high risk of bias') (Higgins 2011).

We would also have evaluated the risk of attrition bias, as estimated by the percentage of participants lost to follow-up. We would have excluded from the meta-analysis trials with a total attrition of more than 20% or with between-group differences in attrition exceeding 10%, but would still have included them in the review.

Summary of findings tables

We used the Grading of Recommendations Assessment, Development and Evaluation (GRADE) approach to assess the quality of the body of evidence (Guyatt 2011b). The GRADE approach classifies the quality of a body of evidence based on the extent to which one can be confident that an estimate of effect or association reflects the outcome being assessed (Balshem 2011; Guyatt 2011a; Guyatt 2011c; Guyatt 2011d; Guyatt 2011e; Guyatt 2011f; Guyatt 2011g; Guyatt 2011h).

The Summary of findings for the main comparison, created with GRADE software (GRADEPro 2008), includes health-related quality of life, fatigue, hemoglobin at the end of the study, adverse events, withdrawals due to adverse events, withdrawals due to lack of efficacy, and withdrawals due to high blood pressure.

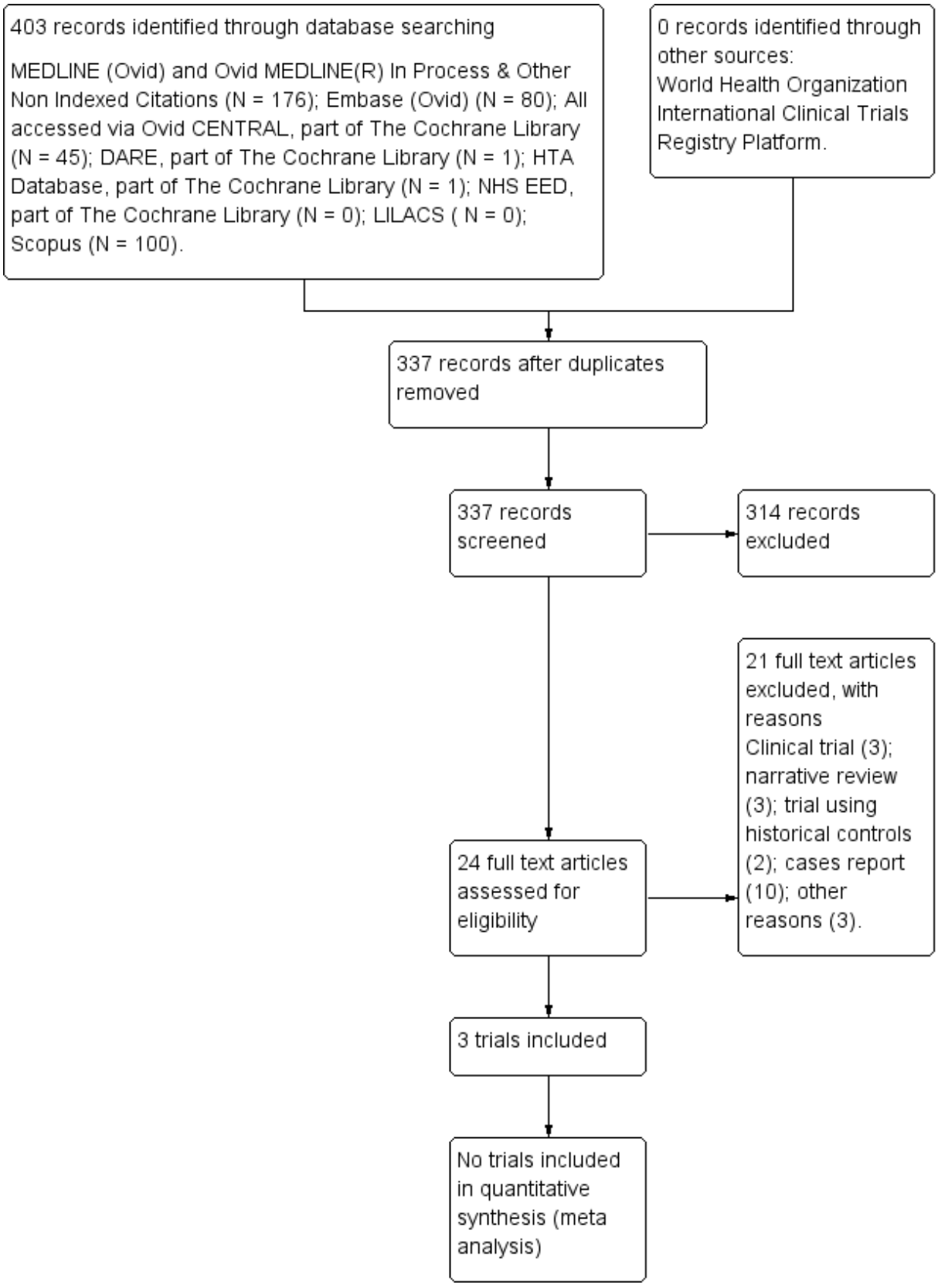
RESULTS

Description of studies

Results of the search

We identified 337 references using our search strategy (Figure 1). Three trials with a total of 133 participants met our inclusion criteria (Nordström 1997; Peeters 1996; Pincus 1990).

Figure 1. Study flow diagram (7 August 2012).



Included studies

Interventions and populations assessed in the trials

The three trials reported on EPO compared with placebo (Nordström 1997; Peeters 1996; Pincus 1990). Two trials used a subcutaneous route of administration (Nordström 1997; Peeters 1996), and one trial administered EPO by an intravenous route (Pincus 1990). The subcutaneous EPO regimen varied from 150 IU/kg-body (Nordström 1997) to 240 IU/kg-body (Peeters 1996). The intravenous EPO trial administered the intervention at 50 U/kg, 100 U/kg, and 150 U/kg doses (Pincus 1990). The mean percentage of female participants was 88.17 (± 5.09), with a mean age of 56.43 (± 3.38) years.

Location and timing of trials

The trials were published between 1990 and 1997. They were conducted in Sweden (Nordström 1997), the Netherlands (Peeters 1996), and the USA (Pincus 1990).

Trial methods

All three trials were conducted using a parallel study design. The trials were small with sample sizes ranging from 17 to 70, with a median sample size of 46 and a mean of 44.33 (± SD 26.54), and were conducted without a priori sample size estimation. The follow-ups ranged from eight to 52 weeks. . Two trials were multicenter (Nordström 1997; Pincus 1990), and the setting unclear for Peeters 1996.

The Characteristics of included studies table shows a detailed description of the trials (Nordström 1997; Peeters 1996; Pincus 1990).

Excluded studies

Twenty-one studies were excluded (Arndt 2005; Birgegard 1991; Dyjas 2005; Fantini 1992; Goodnough 1997; Kaltwasser 2001; Kato 1994; Krantz 1995; Matsuda 2001; Means 1989; Mercuriali 1996; Mercuriali 1997; Murphy 1994; Pettersson 1993a; Saikawa 1994; Salvarani 1991; Swaak 1994; Takashina 1990; Tauchi 1990; Vreugdenhil 1990; Vreugdenhil 1992). See Characteristics of excluded studies table for reasons for exclusion.

Risk of bias in included studies

The risks of bias in the included trials are summarised in Figure 2 and Figure 3, and are detailed in the Characteristics of included studies table.

Figure 2. Risk of bias graph: review authors' judgements about each risk of bias item presented as percentages across all included studies.

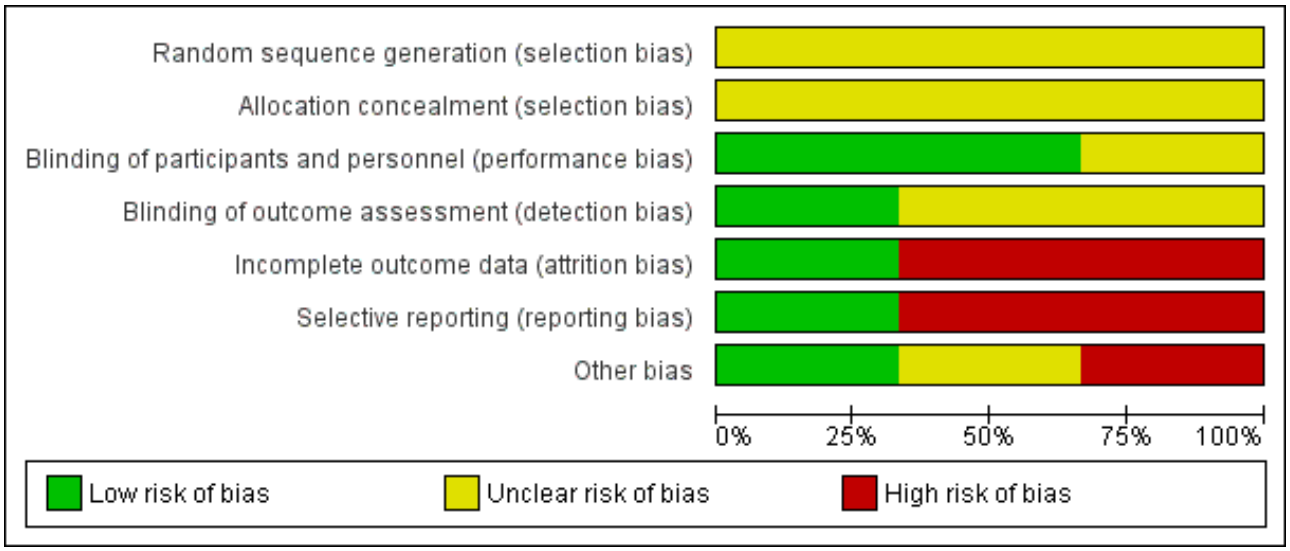
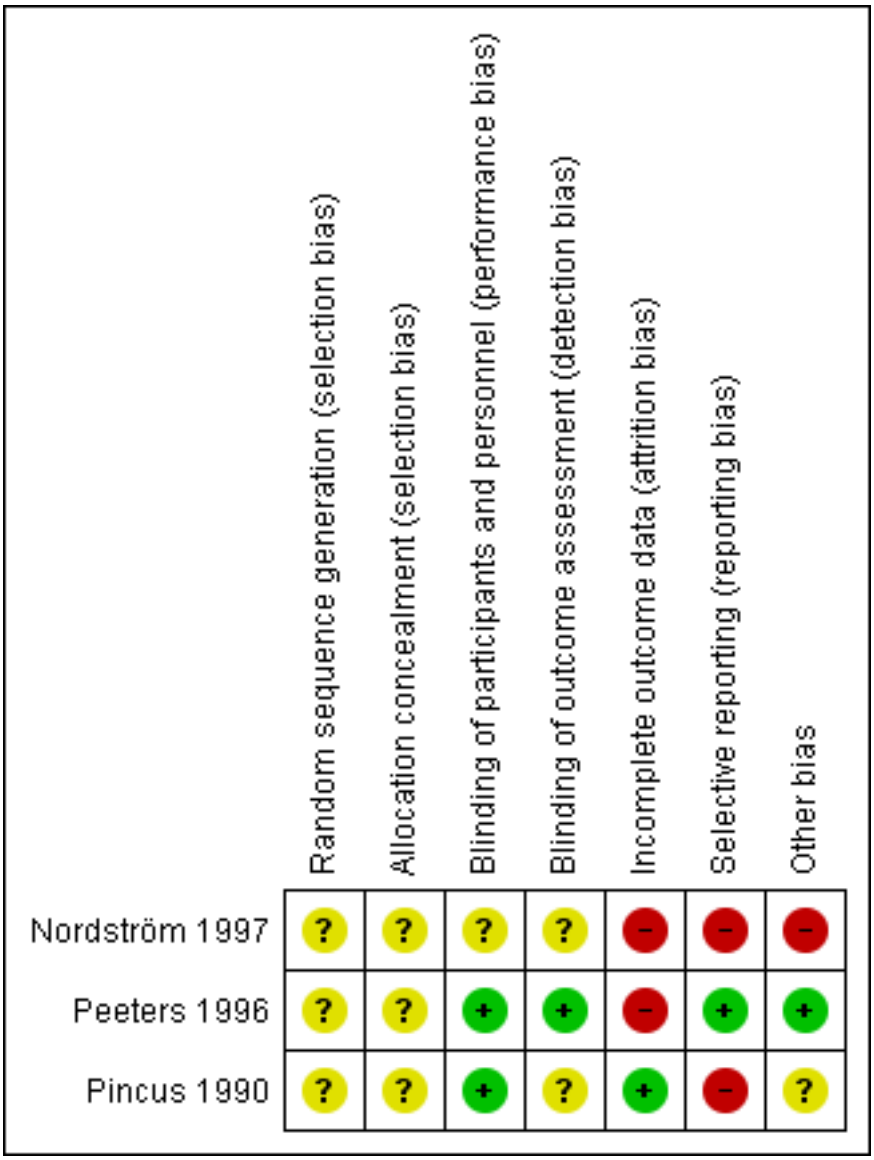


Figure 3. Risk of bias summary: review authors' judgements about each risk of bias item for each included study.



Allocation

Random Sequence Generation
The risk of bias arising from the method of generation of the allocation sequence was unclear in all trials (Nordström 1997; Peeters 1996; Pincus 1990).

Allocation Concealment
The risk of bias arising from the method of allocation concealment was unclear in all trials (Nordström 1997; Peeters 1996; Pincus 1990).

Blinding

The risk of bias due to blinding of participants and personnel was low in two trials because the drug preparations were covered to make them indistinguishable (Peeters 1996; Pincus 1990). The risk of bias was unclear in the remaining trial (Nordström 1997).

The risk of bias arising from lack of blinding of outcome assessment was low in one trial (Peeters 1996). The risk of bias was unclear in the remaining trials (Pincus 1990; Nordström 1997).

Incomplete outcome data

The risk of attrition bias was low in one trial (Pincus 1990). The risk of attrition bias was high in the remaining trials (Nordström 1997; Peeters 1996).

Selective reporting

The risk of reporting bias was low in one trial (Peeters 1996). The risk of reporting bias was high in the remaining trials (Nordström 1997; Pincus 1990).

Other potential sources of bias

One study (Nordström 1997) had high risk of bias for baseline imbalance between comparison groups for gender, duration of disease (years) and medication for treating ARA clinical variables.

Pincus 1990 did not report baseline characteristics of the patients assigned to the placebo group, and there was no baseline imbalance in Peeters 1996. All included trials were suspected to have sponsorship bias, as they were funded by the pharmaceutical company, but we do not have enough information to permit judgment of 'low risk' or 'high risk' for inappropriate influence.

Effects of interventions

See: **Summary of findings for the main comparison** Erythropoietin (subcutaneous or intravenous at varying dosages) compared to placebo for anemia in patients with rheumatoid arthritis

Results are based on three randomized controlled trials (Nordström 1997; Peeters 1996; Pincus 1990). Summary of findings for the main comparison shows evidence on outcomes reported by the trials.

Health-related quality of life

Nordström 1997 reported a significant elevation of energy at the end of the study after week 12 (P = 0.004). Otherwise, Stanford Health Assessment Questionnaire scores, Nottingham Health Profile scores, classification of functional class or joint score index scores did not differ significantly between the comparison groups.

Peeters 1996, reporting patients' global assessment (VAS score 0 to 10), found statistically significant differences comparing the EPO group (median 3.5 and interquartile range 1.0 to 6.0) to placebo (median 4.5 and interquartile range 2.0 to 7.5) at 52 weeks (P = 0.027).

Pincus 1990 assessed patient satisfaction in activities of daily living, using the modified Stanford Health Assessment Questionnaire, and found no significant differences between comparison groups during the trial duration; however, it did not report supporting data.

Fatigue

This outcome was not assessed by any of the trials included in this review.

Safety (Adverse events including adverse drug reaction)

Nordström 1997 found no significant alterations in pulse, blood pressure, platelet counts, albumin, creatinine, alanine aminotransferase, or aspartate aminotransferase values. Peeters 1996 found no significant rise in blood pressure and thromboembolic complications. Pincus 1990 found no adverse events associated with EPO.

Hemoglobin level at the end of the study

Nordström 1997 (46 participants) reported a statistically significant increase in hemoglobin level at 12 weeks in the EPO group compared with the placebo group (mean difference (MD) 8.00, 95% confidence interval (CI) 7.43 to 8.57; P = 0.00001) .

Peeters 1996 (70 participants) reported a statistically significant increase in hemoglobin level at 52 weeks in the EPO group (median 134; interquartile range 110 to 158 g/litre) compared with the placebo group (median 112; interquartile range 86 to 128 g/litre; P = 0.001).

Pincus 1990 (17 participants) reported no significant difference between the EPO and placebo groups (MD 4.69, 95% CI -0.17 to 9.55; P = 0.06).

Withdrawals due to adverse events

Nordström 1997 reported no serious adverse effects causing premature discontinuation. This outcome was not reported by the other two trials (Peeters 1996; Pincus 1990).

Withdrawals due to lack of efficacy

This outcome was not assessed by the trials.

Withdrawals due to high blood pressure

This outcome was not assessed by the trials.

Withdrawals due to high disease activity

Peeters 1996, with eight events in 70 participants, reported no significant difference between the EPO and placebo groups (risk ratio (RR) 0.64, 95% CI 0.16 to 2.46, P = 0.51). The other two trials did not report this outcome (Nordström 1997; Pincus 1990).

Withdrawals due to poor compliance

Peeters 1996, with four events in 70 participants, reported no significant difference between the EPO and placebo groups (RR 1.06, 95% CI 0.16 to 7.10, P = 0.95). The other two trials did not report this outcome (Nordström 1997; Pincus 1990).

DISCUSSION

Summary of main results

This review of erythropoiesis-stimulating agents for treating anemia in patients with rheumatoid arthritis identified three randomized controlled trials incorporating 133 participants (Nordström 1997; Peeters 1996; Pincus 1990). Trials assessed EPO with different follow-ups (eight weeks (Pincus 1990), 12 weeks (Nordström 1997) and 52 weeks (Peeters 1996)) compared with placebo. Two trials administered EPO by a subcutaneous route (Nordström 1997; Peeters 1996), and one used an intravenous route (Pincus 1990). The trials were conducted in developed countries (Sweden, the Netherlands, and the USA). Two trials found benefits for health-related quality of life at 12 and 52 weeks (Nordström 1997; Peeters 1996). Two trials found benefits in increasing hemoglobin levels at 12 and 52 weeks (Nordström 1997; Peeters 1996). All trials had high risks of bias, were underpowered, and were sponsored by the pharmaceutical company. The safety profile of human recombinant erythropoietin is unclear over the course of the trials. See Summary of findings for the main comparison for details.

Overall completeness and applicability of evidence

This Cochrane review provides inconclusive evidence on the assessed intervention, due both to heterogeneity between trials, and to inadequate information provided by trial reports (Hopewell 2010). During this review, we have identified the following issues, which we feel are particularly relevant to consider as further work is planned. Overall, heterogeneity between trials prevented the pooling of results, with the main areas of variation between trials being differences in outcome definition, and inconsistency of reported outcomes i.e., one trial reported

hemoglobin level (Nordström 1997) and another trial reported hematocrit (Pincus 1990). It was not advisable to pool data on the health-related quality of life and hemoglobin level at the end of the study, due to inconsistency in reporting the results of these outcomes. It has been suggested that trials should adopt an agreed set of core outcomes for each medical condition (Clarke 2007). This approach may reduce the impact of outcome reporting bias (Kirkham 2010). There is an international network initiated in 1992 aimed at improving outcome measurement in rheumatology, named 'Outcome Measures in Rheumatoid Arthritis Clinical Trials' (OMERACT) (Tugwell 2007). A standardized definition of rheumatoid arthritis flare is needed for research and clinical care that combines both clinician and patient perspectives (Alten 2011; Bartlett 2012; Bingham 2011).

Another approach to reduce the impact of outcome reporting bias may be to adopt the recommendations of the Patient-Centered Outcomes Research Institute (PCORI) (PCORI 2012). It was established by the United States Congress as an independent, non-profit organization, created to conduct research to provide information about the best available evidence to help patients and their healthcare providers make more informed decisions. PCORI's research is intended to give patients a better understanding of the prevention, treatment and care options available, and the science that supports those options (Basch 2012; Gabriel 2012; PCORI 2012).

Quality of the evidence

The three randomized controlled trials included in this review all had a high risk of bias. The main source of bias was the lack of detail in describing the generation of randomization sequences or the allocation concealment. The trials also lacked detail about their blinding processes, but two of them described 'similar placebos' (Peeters 1996; Pincus 1990). Peeters 1996 was masked to outcome assessment. In this clinical setting, the potential harms of EPO are unknown, due to the lack of detail in presenting safety data. All the trials were underpowered, and were sponsored by the pharmaceutical industry, which reduces confidence in the results. Summary of findings for the main comparison shows the quality of the evidence supplied by the included trials.

Potential biases in the review process

In the process of conducting a systematic review, there is a group of biases called significance-chasing biases (Ioannidis 2010). These includes publication bias, selective outcome reporting bias, selective analysis reporting bias, and fabrication bias (Ioannidis 2010). Publication bias represents a major threat to the validity of systematic reviews, particularly in reviews that include small trials. However, we believe that this Cochrane review has a low risk of publication bias, due to the thorough trial search process. Selective outcome reporting bias operates through suppression of information on specific outcomes and has similarities to study publication bias, in that 'negative' results remain unpublished (Ioannidis 2010). This Cochrane review found that two trials had high risk of selective outcome reporting (Nordström 1997; Pincus 1990).

AUTHORS' CONCLUSIONS

Implications for practice

We found eligible randomized controlled trials only assessing human recombinant erythropoietin. They provide evidence of benefit in improving health-related quality of life and in increasing hemoglobin levels. The results are based on trials with a high risk of bias, which were sponsored by the pharmaceutical company. The safety profile of human recombinant erythropoietin is unclear in this population. The trial results should therefore be treated with great caution.

Implications for research

This review highlights a need for well-designed, high-quality randomized trials, with a priori calculations on sample sizes, to assess the benefits and harms of erythropoiesis-stimulating agents for anemia in rheumatoid arthritis. The trials should include outcomes such as quality of life measures, fatigue, adverse events, and hemoglobin level at the end of the study. The trials should be conducted according to 'Outcome Measures in Rheumatoid Arthritis Clinical Trials' (OMERACT) recommendations for rheumatoid arthritis (Alten 2011; Bartlett 2012; Bingham 2011; Tugwell 2007) and the Patient-Centered Outcomes Research Institute (PCORI) recommendations (Basch 2012; Gabriel 2012; PCORI 2012).

Rheumatoid arthritis is a chronic inflammatory state characterized by high circulating levels of interleukin-6, which is the main factor causing anemia in this population; patients suffering from this disorder should therefore be treated with disease-modifying antirheumatic drugs (DMARDs), but EPO could still be an issue in countries where DMARDs are not yet accessible. Potential trials for assessing benefits and harms of erythropoiesis-stimulating agents to treat anemia in rheumatoid arthritis should be reported according to the Consolidated Standards of Reporting Trials (CONSORT) statement for improving the quality of reporting of efficacy and of harms in clinical research (Ioannidis 2004; Moher 2010).

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* Indicates the major publication for the study

CHARACTERISTICS OF STUDIES

Characteristics of included studies *[ordered by study ID]*

Nordström 1997

Methods	1. Design: parallel-design (2 arms) 2. Country: Sweden (7 sites) 3. Intention-to-treat analysis: no 4. Follow-up period: 12 weeks 5. Unit of randomization: patient 6. Unit of analysis: patient
Participants	1. Randomized: 46 (Quote "three active, one placebo") (page 68)

Nordström 1997 *(Continued)*

Erythropoietin (EPO) group: 36
Placebo group: 10

2. Patients receiving drug: 46
EPO group: 36 (78.2%)
Placebo group: 10 (21.7%)

3. Analyzed patients:
EPO group: 26 (72.2%)
Placebo group: 9 (90%)
Imbalance between groups: 17.8%

4. Age (years; mean±SD; range)
EPO group: 56.1±12.7; 25 to 76
Placebo group: 56.9±12.7; 29 to 79

5. Gender (female):
Overall: 85% (39/46)
EPO group: 80.5% (29/36)
Placebo group: 100% (10/10)

6. Inclusion criteria:

- Clinical diagnosis of rheumatoid arthritis by American College of Rheumatology (ACR) criteria.
- Independent of disease activity with stable disease.
- The Disease-Modifying Anti-rheumatic Drugs (DMARDs) regimens unchanged during the treatment.
- Hemoglobin concentrations below ≤ 100 g/L (women) and ≤ 110 g/L (men).
- Hemoglobin concentrations during iron supplementations did not increase by more than 15 g/L.

7. Exclusion criteria:

- Hemorrhage.
- Hemolysis.
- Folic acid deficiency.
- Vitamin B_{12} deficiency.
- Uncontrolled hypertension.
- Kidney disease.
- Liver disease.
- High doses of corticosteroids (exceeding 10 mg of prednisone or equivalent).

Interventions	1. Interventional group: recombinant human erythropoietin (rHuEPO; Express 10,000 U/ml, Cilag AB Sweden), 150 IU/ kg subcutaneous injected twice weekly. Duration: 12 weeks. 2. Placebo: subcutaneous injection twice weekly for 12 weeks. Nature of placebo: not given. 3. Co-intervention: oral iron supplementations at a median dose of 200 mg elemental iron per day.
Outcomes	Outcomes were not defined explicitly as primary or secondary: 1. An adequate response was defined as reaching an Hb≥ 120 g/L at least once after the study start (page 68). 2. Elevation of energy level (page 70). 3. Safety (page 71).
Notes	1. Sample size calculation a priori: not reported. 2. Sponsor: Cilag AB Sweden. 3. Roll of sponsor: not specified. 4. Conflict of interest: not described.

Risk of bias

Nordström 1997 *(Continued)*

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Quote: “Randomization was carried out in blocks of four patients (three active, one placebo) and allocation within each block was in random order” (page 68). Insufficient information to consider 'low risk' or 'high risk'. Comment: there is an imbalance in gender and duration of disease variables (page 69, table 1).
Allocation concealment (selection bias)	Unclear risk	Insufficient information to permit judgment of 'low risk' or 'high risk'.
Blinding of participants and personnel (performance bias) All outcomes	Unclear risk	Insufficient information to permit judgment of 'low risk' or 'high risk'. This trial was reported as double-blind.
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	Insufficient information to permit judgment of 'low risk' or 'high risk'. This trial was reported as double-blind.
Incomplete outcome data (attrition bias) All outcomes	High risk	1. Lost postrandomization: 24% (11/46). EPO group: 38.4% (10/26). Placebo group: 11.1% (1/9). 2. Imbalance between comparison groups: 27.3% Quote: "(5 patients excluded due to entering the extension study, 5 drop-outs) patients receiving rHuEPO over 9 patients receiving placebo (one drop out)" (page 70) 3. Comment: potentially inappropriate application of simple imputation. 4. Comment: For continuous outcome data, plausible effects size (difference in means or standardized difference in means) among missing outcomes enough to induce clinically relevant bias in observed effect size and potentially inappropriate application of simple imputation.
Selective reporting (reporting bias)	High risk	Quote: "A significant rise in Hb was noted in 26 (5 patients excluded due to entering the extension study, 5 drop-outs) patients receiving rHuEPO over 9 patients receiving placebo (one drop-out) (Hb elevation from 95 g/L to 107 g/L vs 93 g/L to 97 g/L, $P < 0.05$), from week 10 onwards that lasted throughout the study. A significant elevation of red blood cells was noted already from 4 weeks onward ($P = 0.02$) and Hct levels at week 12 ($P = 0.009$)" (page 70) Quote: "only 14.6% (N = 6) of the patients were considered responders according to the preset criteria of Hb level equaling or exceeding 120 g/l" (page 70). Quote "A significant elevation of energy (NHP variable) was noted at the end of the study after week 12 ($P = 0.004$). Otherwise, HAQ scores, NHP scores, classification of functional class or joint score index scores did not differ significantly between the two groups". (page 70). Comment: one or more outcomes of interest in the review are reported incompletely so that they cannot be entered in a meta-analysis.
Other bias	High risk	Comments: 1. There is imbalance between comparison groups regarding gender, duration of disease (years) and medication for treating ARA variables (page 69).

Nordström 1997 *(Continued)*

	2. There was a potential source of bias related to the specific study design used, with extreme baseline imbalance.

Peeters 1996

Methods	1. Design: parallel design (2 arms) 2. Country: Netherlands 3. Multicenter study: unclear. 4. Intention-to-treat analysis: yes 5. Per protocol analysis: yes 6. Follow-up period: 52 weeks 7. Unit of randomization: patient 8.Unit of analysis: patient
Participants	1. Randomized: 70 Erythropoietin (EPO) group: 34 Placebo group: 36 2. Age: years; median 5th to 95th centile EPO group: 56; 23 to 79 Placebo group: 58; 39 to 75 3. Gender (female): EPO group: 79% (27/34) Placebo group: 86% (31/36) 4. Inclusion criteria: • Age 18 years or older. • Clinical diagnosis of rheumatoid arthritis by American College of Rheumatology (ACR) criteria (functional class I, II, III). Active disease defined as a minimum of nine swollen joints and a Richie score of 9. • Anemia of chronic disease for a minimum duration of three months. • Hemoglobin concentrations below 117 g/L (for both men and women), without signs of vitamin and iron deficiency, blood loss, hemolysis, or other hematological disorder. 5. Exclusion criteria: • Patient receiving azathioprine, cyclophosphamide or cyclosporine • Signs of vitamin deficiency • Signs of iron deficiency • Blood loss • Hemolysis • Hematological disorders • History of thromboembolic events • History of epileptic fits • Uncontrolled hypertension • Renal disease • Liver disease
Interventions	1. Intervention group: recombinant human erythropoietin (rHuEPO), 240 U per kg subcutaneous (sc) initially three times a week. Duration: 52 weeks. 2. Placebo: visually similar. Composition of placebo was not reported.

Peeters 1996 *(Continued)*

	3. Co-intervention: oral iron supplementation. Quote "Adjusment of the dose of disease modifying antirheumatic drugs or prednisone, as well as local measures, particularly intra-articular corticosteroids injections, was not allowed during the study (page 740)
Outcomes	1. Primary: • Hemoglobin measurements • Primary disease activity measure assessed by modified Paulus index (See Appendix 9) 2. Secondary: • Ritchie index • The number of swollen joints • Patient's global assessment • Westergren Erythro Sedimentation Rate • Pain score (1 to 10) • C-reactive protein concentration
Notes	1. Sample size calculation a priori: not reported. 2. Sponsor: Dutch League against Rheumatism (Het Nationaal Rheuma Fonds). 3. Sponsor: Boehringer Mannheim provided rHuEPO. 4. Conflict of interest: not reported.

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Quote " randomisation of the patients...was done by a second independent observer" (page 740). Insufficient information to permit judgment of 'low risk' or 'high risk'.
Allocation concealment (selection bias)	Unclear risk	Quote: 'Randomisation of the patients ... was done by a second independent observer.' Insufficient information to permit judgment of 'low risk' or 'high risk'.
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Quote: "The placebo group received a visually similar placebo. After randomisation, patients in the placebo group were matched with patients in the treatment group and followed their treatment regime with respect to frequency of administration".
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Quote: "Disease activity measures were assessed by the first observer, who remained blinded for treatment schedules and laboratory results" (page 740).
Incomplete outcome data (attrition bias) All outcomes	High risk	1. Overall: 82.8% (58/70) 2. EPO group: 85% (29/34) 3. Placebo group: 80% (29/36) 4. Imbalance between groups: 5% Comment: Missing outcome data balanced in numbers across intervention groups, with similar reasons for missing data across groups. However, this was a small trial.

Peeters 1996 *(Continued)*

Selective reporting (reporting bias)	Low risk	This trial reported outcomes of clinical interest.
Other bias	Low risk	Quote: "At baseline, groups were compared using Student's t test, the Mann-Whitney test, and the x' test where appropriate." There was no significant baseline imbalance.

Pincus 1990

Methods	1. Design: parallel design (2 arms). 2. Multicenter study: USA (5 sites). 3. Intention-to-treat analysis: yes. 4. Follow-up period: 8 weeks. 5. Follow-up period: 24 weeks open label. 6.- Unit of randomization: patients 7.- Unit of analysis: patient.
Participants	1. Randomized: 17 Erythropoietin (EPO) group: 13 Placebo group: 4 2. Receiving EPO and placebo: 17 EPO group:13 Placebo group: 4 3. Age: years; mean range Both groups: 52; 25 to 73 By comparison group: not reported 4. Gender (female): Both group: 94.1% (16/17) By comparison group: not reported 5. Inclusion criteria: These were not reported explicitly. Quote: " All met the 1958 American Rheumatism Association criteria for rheumatoid arthritis... were being treated only with nonsteroidal anti-inflammatory drugs and no patient was taking gold, methotrexate, azathioprine, penicillamine, or prednisone, or had taken any second-line agents for 6 months prior to, or during, erythropoietin administration" (page 162). 6. Exclusion criteria: • Renal disease • History of seizure • Uncontrolled hypertension • Severe allergic reactions • Asthma • Active hepatitis • Other inflammatory conditions • Malignancy • Ischemic heart disease • Active peptic ulcer within one month of the study • Neutropenia

Pincus 1990 *(Continued)*

- Hemolytic anemia
- Thrombocytopenia

Interventions	1. Intervention group: recombinant human erythropoietin rHuEPO (50, 100, 150 U per kg three times a week, intravenous bolus given over a 5 minute period for up to 8 weeks). 2. Placebo: schedule identical to intervention. Placebo composition was not reported. 3. Co-intervention: oral ferrous sulphate (325 mg three times daily).
Outcomes	This trial did not explicitly address this domain. 1. Change in hematocrit, and leucocyte and platelet counts (page 163) 2. Safety (page 163) 3. Rheumatologic clinical status changes (page 165)
Notes	1. Sample size calculation a priori: not reported. 2. Sponsor: Ortho Biotech Corporation, National Institutes of Health (grants DK-1555, RR-95, and T32-07186), Jack C Massey Foundation, and Veterans Administration Medical Research Funds. 3. Role of sponsor: Ortho Biotech Corporation provided the intervention. 4.- This study had two phases: First phase: 8 weeks randomized double blind study. Second Phase: 24 week-open-label-study "involved an open-label protocol in which all patients received erythropoietin three times weekly" (page 163). Quote: "Following the 8 week randomized study, the 17 patients were offered the possibility of participations in a 24 week open-label extension study" (page 162). 5. Conflict of interest: not described.

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Insufficient information to consider 'low risk' or 'high risk'. Comment: there is imbalance between comparison groups regarding treated number of patients (13 treated with EPO and 4 with placebo).
Allocation concealment (selection bias)	Unclear risk	Insufficient information to consider 'low risk' or 'high risk'.
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Quote: "identically appearing placebo" (page 162)
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	Insufficient information to consider 'low risk' or 'high risk'.
Incomplete outcome data (attrition bias) All outcomes	Low risk	No missing outcome data.

Pincus 1990 *(Continued)*

Selective reporting (reporting bias)	High risk	One or more outcomes of interest in the review are reported incompletely, so that they cannot be entered in a meta-analysis. Comment: this trial reported only activities of daily living score and visual analog pain scale score data for intervention group. (page162).
Other bias	Unclear risk	Comment: this trial did not report baseline characteristics of the patients assigned to placebo group.

Characteristics of excluded studies *[ordered by study ID]*

Study	Reason for exclusion
Arndt 2005	Clinical trial but not an RCT
Birgegard 1991	Case report
Dyjas 2005	Controlled clinical trial but not an RCT
Fantini 1992	Case report
Goodnough 1997	Narrative review of the responses to erythropoietin in patients with rheumatoid arthritis
Kaltwasser 2001	Clinical trial but not an RCT
Kato 1994	Trial was conducted using historical controls
Krantz 1995	Narrative review of erythropoietin and the anemia of chronic disease
Matsuda 2001	Trial included patients without anemia
Means 1989	Case report
Mercuriali 1996	Narrative review of erythropoietin alpha for autologous blood donations in patients with rheumatoid arthritis and concomitant anemia
Mercuriali 1997	Trial was conducted using historical controls
Murphy 1994	This study is shown as RCT involving 20 participants (10 assigned to EPO versus 10 randomized to placebo). Quote "Intervention group: recombinant human erythropoietin (rHuEPO) "starting at 40 IU per kg (patients *1-10*) and 100 U/Kg (patients *11-20*)" (page 1337), subcutaneous (sc), twice a week by 20 weeks". Therefore, it must be considered as non-randomized.
Pettersson 1993a	Case report
Saikawa 1994	Study including anemic and non-anemic with rheumatoid arthritis. All participants received erythropoietin.
Salvarani 1991	Case report
Swaak 1994	Case report

Study	Reason for exclusion
Takashina 1990	Case report
Tauchi 1990	Case report
Vreugdenhil 1990	Case report
Vreugdenhil 1992	Case report

APPENDICES

Appendix 1. American Rheumatology criteria of rheumatoid arthritis

Source: Arnett 1988

1. Morning stiffness in and around joints lasting at least 1 hour before maximal improvement;
2. Soft tissue swelling (arthritis) of 3 or more joint areas observed by a physician;
3. Swelling (arthritis) of the proximal interphalangeal, metacarpophalangeal, or wrist joints;
4. Symmetric swelling (arthritis);
5. Rheumatoid nodules;
6. The presence of rheumatoid factor;
7. Radiographic erosions and/or periarticular osteopenia in hand and/or wrist joints.

Criteria 1 through 4 must have been present for at least 6 weeks.
Rheumatoid arthritis is defined by the presence of 4 or more criteria, and no further qualifications (classic, definite, or probable) or list of exclusions are required.

Appendix 2. World Health Organization

Source: WHO 2008

2.1.- Hemoglobin: <120 g/l (12 g/dl) for non-pregnant women (≥15 years).

2.2.- Hemoglobin: <130 g/l (13 g/dl) for men(≥15 years).

Appendix 3. Ovid Medline search strategy

1. exp arthritis, rheumatoid/

2. ((rheumatoid or reumatoid or revmatoid or rheumatic or reumatic or revmatic or rheumat$ or reumat$ or revmarthrit$) adj3 (arthrit$ or artrit$ or diseas$ or condition$ or nodule$)).tw.

3. (felty$ adj2 syndrome).tw.

4. (caplan$ adj2 syndrome).tw.

5. (sjogren$ adj2 syndrome).tw.

6. (sicca adj2 syndrome).tw.

7. still$ disease.tw.

8. bechterew$ disease.tw.

9. or/1-8

10. exp Hematinics/

11. hematinic$.tw.

12. hematopoietic$.tw.

13. erythropoie$.tw.

14. (esa or esas).tw.

15. rhuepo.tw.

16. (epoetin adj (alpha or alfa or beta)).tw.

17. Abseamed.tw.

18. Binocrit.tw.

19. Culat.tw.

20. Dynepo.tw.

21. EPIAO.tw.

22. Epog?en.tw.

23. Epokine.tw.

24. Epomax.tw.

25. Epopen.tw.

26. Eporon.tw.

27. Eposino.tw.

28. Epotin.tw.

29. Epotrex.tw.

30. Epovitan.tw.

31. Epoxitin.tw.

32. Eprex.tw.

33. Erantin.tw.

34. Eritina.tw.

35. Eritrogen.tw.

36. Eritromax.tw.

37. Erypo.tw.

38. Exetin-A.tw.

39. Globuren.tw.

40. Hemapo.tw.

41. Hemax-Eritron.tw.

42. Hemax.tw.

43. Hemoprex.tw.

44. Hepta.tw.

45. Hypercrit.tw.

46. Mepotin.tw.

47. Mircera.tw.

48. Negortire.tw.

49. NeoRecormon.tw.

50. Procrit.tw.

51. Recormon.tw.

52. Renogen.tw.

53. Repotin.tw.

54. Retacrit.tw.

55. Silapo.tw.

56. Tinax.tw.

57. Wepox.tw.

58. Yepotin.tw.

59. or/10-58

60. randomized controlled trial.pt.

61. controlled clinical trial.pt.

62. randomized.ab.

63. placebo.ab.

64. drug therapy.fs.

65. randomly.ab.

66. trial.ab.

67. groups.ab.

68. or/60-67

69. (animals not (humans and animals)).sh.

70. 68 not 69

71. and/9,59,70

Appendix 4. Ovid EMBASE

1. exp arthritis, rheumatoid/

2. ((rheumatoid or reumatoid or revmatoid or rheumatic or reumatic or revmatic or rheumat$ or reumat$ or revmarthrit$) adj3 (arthrit$ or artrit$ or diseas$ or condition$ or nodule$)).tw.

3. (felty$ adj2 syndrome).tw.

4. (caplan$ adj2 syndrome).tw.

5. (sjogren$ adj2 syndrome).tw.

6. (sicca adj2 syndrome).tw.

7. still$ disease.tw.

8. or/1-7

9. exp antianemic agent/

10. hematinic$.tw.

11. hematopoietic$.tw.

12. erythropoie$.tw.

13. (esa or esas).tw.

14. rhuepo.tw.

15. (epoetin adj (alpha or alfa or beta)).tw.

16. Abseamed.tw.

17. Binocrit.tw.

18. Culat.tw.

19. Dynepo.tw.

20. EPIAO.tw.

21. Epog?en.tw.

22. Epokine.tw.

23. Epomax.tw.

24. Epopen.tw.

25. Eporon.tw.

26. Eposino.tw.

27. Epotin.tw.

28. Epotrex.tw.

29. Epovitan.tw.

30. Epoxitin.tw.

31. Eprex.tw.

32. Erantin.tw.

33. Eritina.tw.

34. Eritrogen.tw.

35. Eritromax.tw.

36. Erypo.tw.

37. Exetin-A.tw.

38. Globuren.tw.

39. Hemapo.tw.

40. Hemax-Eritron.tw.

41. Hemax.tw.

42. Hemoprex.tw.

43. Hepta.tw.

44. Hypercrit.tw.

45. Mepotin.tw.

46. Mircera.tw.

47. Negortire.tw.

48. NeoRecormon.tw.

49. Procrit.tw.

50. Recormon.tw.

51. Renogen.tw.

52. Repotin.tw.

53. Retacrit.tw.

54. Silapo.tw.

55. Tinax.tw.

56. Wepox.tw.

57. Yepotin.tw.

58. or/9-57

59. 8 and 58

60. (random$ or placebo$).ti,ab.

61. ((single$ or double$ or triple$ or treble$) and (blind$ or mask$)).ti,ab.

62. controlled clinical trial$.ti,ab.

63. RETRACTED ARTICLE/

64. or/60-63

65. (animal$ not human$).sh,hw.

66. 64 not 65

67. 59 and 66

Appendix 5. LILACS search strategy

rheumatoid OR rheumatoid OR revmatoid OR rheumatic OR rheumatic OR revmatic OR reumat* OR revmarthrit* in Words

AND

hematinic* hematopoietic* or erythropoie* or rhuepo or epoetin in Words

Appendix 6. Scopus search strategy

#1 rheumatoid OR rheumatoid OR revmatoid OR rheumatic OR rheumatic OR revmatic OR reumat* OR revmarthrit*in TITLE-ABS-KEY

#2 hematinic* OR hematopoietic*OR erythropoie* OR rhuepo OR epoetin in TITLE-ABS-KEY

#3 #1 AND #2

#4 #3 limited to Conference Paper

Appendix 7. World Health Organization International Clinical Trials Registry Platform

#1 rheumatoid OR rheumatoid OR revmatoid OR rheumatic OR rheumatic OR revmatic OR reumat* OR revmarthrit*in Condition

#2 hematinic* OR hematopoietic*OR erythropoie* OR rhuepo OR epoetin in Intervention

Appendix 8. Ovid EBM Reviews

1. exp arthritis, rheumatoid/

2. ((rheumatoid or reumatoid or revmatoid or rheumatic or reumatic or revmatic or rheumat$ or reumat$ or revmarthrit$) adj3 (arthrit$ or artrit$ or diseas$ or condition$ or nodule$)).tw.

3. (felty$ adj2 syndrome).tw.

4. (caplan$ adj2 syndrome).tw.

5. (sjogren$ adj2 syndrome).tw.

6. (sicca adj2 syndrome).tw.

7. still$ disease.tw.

8. bechterew$ disease.tw.

9. or/1-8

10. exp Hematinics/

11. hematinic$.tw.

12. hematopoietic$.tw.

13. erythropoie$.tw.

14. (esa or esas).tw.

15. rhuepo.tw.

16. (epoetin adj (alpha or alfa or beta)).tw.

17. Abseamed.tw.

18. Binocrit.tw.

19. Culat.tw.

20. Dynepo.tw.

21. EPIAO.tw.

22. Epog?en.tw.

23. Epokine.tw.

24. Epomax.tw.

25. Epopen.tw.

26. Eporon.tw.

27. Eposino.tw.

28. Epotin.tw.

29. Epotrex.tw.

30. Epovitan.tw.

31. Epoxitin.tw.

32. Eprex.tw.

33. Erantin.tw.

34. Eritina.tw.

35. Eritrogen.tw.

36. Eritromax.tw.

37. Erypo.tw.

38. Exetin-A.tw.

39. Globuren.tw.

40. Hemapo.tw.

41. Hemax-Eritron.tw.

42. Hemax.tw.

43. Hemoprex.tw.

44. Hepta.tw.

45. Hypercrit.tw.

46. Mepotin.tw.

47. Mircera.tw.

48. Negortire.tw.

49. NeoRecormon.tw.

50. Procrit.tw.

51. Recormon.tw.

52. Renogen.tw.

53. Repotin.tw.

54. Retacrit.tw.

55. Silapo.tw.

56. Tinax.tw.

57. Wepox.tw.

58. Yepotin.tw.

59. or/10-58

71. 9 and 59

Appendix 9. Modified Paulus index

From Paulus 1990.

1. Ritchie index;
2. Number of swollen joints;
3. Duration of morning stiffness;
4. Patients' assessment of disease activity;
5. Observers' assessment of disease activity;
6. Erythrocyte sedimentation rate.

If responses in 4 of 6 selected measures were required for improvement (greater than or equal to 20% of above criteria), and by greater than or equal to 2 grades on a 5-grade scale, or from grade 2 to grade 1 for patient's and physician's overall assessments of current disease severity).

WHAT'S NEW

Date	Event	Description
26 January 2010	Amended	Change of authorship and new contact person. Criteria for inclusion and methods updated.

HISTORY

Protocol first published: Issue 2, 1997
Review first published: Issue 2, 2013

Date	Event	Description
26 January 2010	Amended	The protocol has been changed from all sections.
10 September 2008	Amended	CMSG ID: C122-P
10 September 2008	Amended	Converted to new review format.

CONTRIBUTIONS OF AUTHORS

Conceiving the review (guarantor): Arturo Martí-Carvajal (AMC)

Screening search results: AMC, Luís Agreda-Pérez (LAP), Daniel Simancas (DS)

Screening retrieved papers against inclusion criteria: AMC

Appraising quality of papers: AMC, LAP, DS

Abstracting data from papers: AMC, LAP, Ivan Solà (IS).

Data management for the review: AMC, LAP

Entering data into RevMan 5.1: AMC, IS

Double entry of data: AMC, DS, IS.

Interpretation of data: AMC, IS, LAP, DS.

Statistical analysis: AMC, IS

Writing the review: AMC

Comment and editing of review drafts: AMC, IS, LAP, DS.

DECLARATIONS OF INTEREST

In 2004 Arturo Martí-Carvajal was employed by Eli Lilly to run a four-hour workshop on 'How to critically appraise clinical trials on osteoporosis and how to teach this'. This activity was not related to his work with The Cochrane Collaboration or any Cochrane review.

In 2007 Arturo Martí-Carvajal was employed by Merck to run a four-hour workshop 'How to critically appraise clinical trials and how to teach this'. This activity was not related to his work with The Cochrane Collaboration or any Cochrane review.

Ivan Solà, Luís Agreda-Pérez and Daniel Simancas: none known.

SOURCES OF SUPPORT

Internal sources

- No sources of support supplied

External sources

- Iberoamerican Cochrane Centre, Spain.

  Academic.
- Cochrane Musculoskeletal Group, Canada.

  Academic.

DIFFERENCES BETWEEN PROTOCOL AND REVIEW

1. Assessment of risk of bias of the included RCTs was adapted to the new Cochrane methodology recommendations.
2. We amended the terminology for number of withdrawals due to lack of efficacy, number of withdrawals due to high blood pressure, and number of withdrawals due to adverse events by withdrawals due to lack of efficacy, withdrawals due to high blood pressure, and withdrawals due to high disease activity. This was because these outcomes are binary.
3. We included withdrawals due to high disease activity and withdrawals due to poor compliance.

INDEX TERMS

Medical Subject Headings (MeSH)

Anemia [blood] [*drug therapy] [etiology]; Arthritis, Rheumatoid [blood] [*complications]; Epoetin Alfa; Erythropoietin [adverse effects] [*therapeutic use]; Hematinics [adverse effects] [*therapeutic use]; Hemoglobin A [metabolism]; Randomized Controlled Trials as Topic; Recombinant Proteins [adverse effects] [therapeutic use]

MeSH check words

Humans