ERYTHROPOIETIN FOR ANEMIA IN RHEUMATOID ARTHRITIS
(Protocol)

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BACKGROUND
Rheumatoid arthritis (RA) is a chronic systemic and articular inflammatory disorder of unknown etiology (Zvaifler 1993). Anemia is an extra-articular manifestation of RA with a prevalence between 55-70% (Mowat 1971, Remacha et al 1992). The anemia seen in RA includes: chronic diseases, anemia secondary to blood loss, nutritional deficiency, iron deficiency, hemolysis, drug-related anemia and anemia of chronic renal failure (Mowat 1971, Remacha et al 1992, Tozman 1992). The anemia of RA is most frequently associated with disease activity, and it improves during remission (Vreugdenhil et al 1990, Birgegard et al 1987). Chronic disease anemia (in RA and other disorders) is characterized by a low production of erythrocytes thought to be related to the increment of cytokines production in particular tumor necrosis factor (Stockenhuber et al 1994, Krantz 1994). Erythropoietin (EPO) is the hormone primarily responsible for the regulation of erythropoiesis. In patients with RA, EPO levels increase in response to anemia, but this response is insufficient to restore the numbers of erythrocytes to normal levels (Baer et al 1987, Noe et al 1995). Recombinant human erythropoietin (rHuEPO) has been shown to correct the anemia of patients with end-stage renal disease and may be useful for other disease such as RA (Muirhead et al 1995, DeMarchi et al 1993, Krantz 1995, Abels and Rudnick 1991, Markham Bryson 1995, Salvarani et al 1991, Pettersson et al 1993, Pettersson et al 1990, Tauchi et al 1990, Means et al 1989). A few randomized clinical trials (RCTs) have shown an increase in hemoglobin and red blood cells counts (RBC) after the administration of rHuEPO to patients with RA. Issues to be resolved include the duration and degree of this effect, its impact on the quality of life of patients and potential toxicity. The purpose of this systematic review is to evaluate the scientific evidence in randomized controlled clinical trials related to the use of rHuEPO to treat anemia in patients with RA.

OBJECTIVES
To evaluate the efficacy and toxicity of rHuEPO for the treatment of anemia in patients with RA

CRITERIA FOR CONSIDERING STUDIES FOR THIS REVIEW
Types of studies
Studies selected for further review will include:
1) All randomized control trials (RCTs) and controlled clinical trials (CCTs) using rHuEPO for the treatment of anemia in patients with RA. Control interventions will include placebo or another agent with proven efficacy in the treatment of anemia (e.g. iron, folate supplementation, transfusions etc.)

Types of participants
Two trials including patients 16 years and older with a diagnosis of RA> the specificity of the RA diagnosis will be classified as follows:
a) diagnosis according to American College of Rheumatology criteria (ACR) (Arnett et al 1988).
These include:
1) morning stiffness in and around joints lasting at least 1 hour.
2) soft tissue swelling (arthritis) of 3 or more joint areas observed by a physician.
3) arthritis of the proximal interphalangeal, metacarpophalangeal, or wrist joints.
4) symmetric arthritis.
5) rheumatoid nodules
6) 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.

b) diagnosis on the basis of detailed clinical information
c) reference to RA diagnosis with no additional information

2) patients with anemia defined as:
a) hemoglobin levels < 11 g/dl and/or
b) hematocrit < 36%

Types of intervention
Erythropoietin, Placebo or another agent with proven efficacy in the treatment of anemia (e.g. iron, folate supplementation, transfusions etc.)

Types of outcome measures
3) two different types of outcomes will be considered:
   Efficacy and toxicity of rHuEPO. Regarding the efficacy, it will be measured as changes in hemoglobin and hematocrit levels.
   Toxicity will be assessed considering:
   Number of patients with side effects that have been reported in patients treated with rHuEPO: hypertension, increase of plasma potassium and thrombosis, or reference to side effect in the trial.
   Number of dropouts due to side effects.
   Both efficacy and toxicity will be analyzed. The criteria for the analysis are described below.
   All studies with these characteristics will be reviewed and included in the reference list. Subsequent inclusion of trials in the review will be based on the criteria outlined in the methods section.

SEARCH STRATEGY FOR IDENTIFICATION OF STUDIES
To identify trials of rHuEPO for anemia in patients with RA, electronic and hand searches will be performed. MEDLINE will be searched from 1966 to 1996 using a modified strategy developed by the Cochrane Collaboration search strategy (Dickersin et al 1994). EMBASE will be searched from 1988 to 1996 using a strategy similar to the MEDLINE strategy. Current Contents will be searched for the last six months. All languages will be included in the search strategy. Additional keywords that will be used for this search are: rheumatoid arthritis and erythropoietin.

Hand searches will include:
(i) reference lists of papers retrieved by the electronic searches
(ii) abstracts of the following rheumatology meetings in the last 5 years (1992-1996): American College of Rheumatology, British Society of Rheumatology, International League Against Rheumatism and Canadian Rheumatology Association.

(iv) Principal investigators will be contacted to identify any unpublished trials.

METHODS OF THE REVIEW

1. Criteria for inclusion of trials in the systematic review
In addition to the eligibility criteria for the initial review of studies outlined above, the following criteria will be required for inclusion in the systematic review:
   a. Randomized allocation of patients in the trial. The word 'random' or 'randomization' will be included in the description of the allocation of patients to treatment groups.
   b. Adequate allocation concealment for participants and investigators (double-blind studies).
   c. Adequate description of the interventions including dosages and administration.
   d. Minimum duration of the trial of 2 months.
   e. Description of withdrawals and drop-outs.

2. Quality assessment
Methodological quality will be assessed with the scale proposed by Jadad et al (1996). Three of our inclusion criteria are items in this scale, therefore, all the trials included in the review will have a minimum score of 3.

3. Data extraction
Data will be independently extracted by two blinded observers. Agreement between observers will be assessed using a weighted kappa statistic. Disagreements will be discussed by the 2 reviewers to reach a consensus. If there is no agreement a third reviewer will act as adjudicator. Data will be extracted for: baseline and 3 months, and 6 months and 12 months, if available.

Efficacy: Measures of efficacy will include:
   a) Hematocrit level
   b) Hemoglobin level
   c) Quality of life scores

   Toxicity: Toxicity assessments will include:
   a) Number of patients with side effects.
   b) Number of withdrawals due to side effects.
   c) Total number of drop-outs and withdrawals: this measure will combine withdrawal from toxicity and lack efficacy and patients lost to follow-up.
   d) If available, data will also be retrieved for individual or system-specific side effects.

4. Methods to synthesize data
All the trials to be included in the systematic review will be entered into Review Manager 3.0 (Rev Man 3.0).

For hemoglobin and hematocrit the actual effects will be used: a weighted mean effect difference (WMO) will be calculate for each intervention group, using the inverse of the variance as a weight. For quality of life measures, standardized effects sizes will be estimated (change divided by the baseline standard deviation of the sample).

The results for each intervention group will be weighted by the sample size of the group.

Dichotomous results including dropouts and withdrawals will be summarized as odds ratios (ORs).

The summary OR will be obtained by weighting each individual OR by the inverse of the variance of the estimate for each trial.

The results from the various studies will be tested for heterogeneity using the Q chi square statistic.
Overall effects will only be estimated for groups of trials using the same intervention. As such several individual meta-analyses will be performed. The Cochrane Collaboration does not recommended that comparisons be made between pooled groups based on studies including different intervention, since the power of randomization is then lost. Overall effect will be estimated by meta-analysis using both random effects and fixed effects models. Potential publication bias will be evaluated with inverted funnel plot techniques. A sensitivity analysis will be conducted to evaluate the robustness of the meta-analysis. This analysis will examine the effects of methodological quality and potential differences in drug dosages or administration.

**POTENTIAL CONFLICT OF INTEREST**
None known

**COVER SHEET**

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**SOURCES OF SUPPORT**

External sources of support
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Internal sources of support
- No sources of support supplied

**ADDITIONAL TABLES**
Additional tables are not available for this protocol