Prediction and evaluation of the effect of iron treatment in anaemic RA patients


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SUMMARY In order to predict a haemoglobin (Hb) rise, in response to treatment with iron from simple erythrocyte and serological parameters, we treated 28 anaemic RA patients with oral iron during 6 weeks. Iron deficiency, present in 57% of patients, was assessed by staining a bone marrow aspirate for iron. Response rate in this group was 81% and median Hb increase was 0.8 mmol/l. After 6 weeks 69% of iron deficient patients were still anaemic. Patients without iron deficiency, considered as having anaemia of chronic disease (ACD), showed no significant Hb rise. The finding of a hypochromic microcytic anaemia was associated with a significant Hb rise. MCV showed highest specificity and predictive value (90 and 88%) and ferritin was the most valid predictor of a Hb rise within 6 weeks. Combination of low MCV and low ferritin resulted in a 100% specificity and predictive value indicating that patients with values below cut off point of these variables will definitely respond to treatment. Disease activity tended to decrease after 6 weeks, but this was not correlated with a Hb rise. It was concluded that a Hb rise can be predicted accurately by blood parameters. Using certain combinations, bone marrow aspiration is rarely necessary. Iron treatment is only useful in iron deficient RA patients, although active RA limits maximal Hb rise. In contrast to earlier findings, iron treatment had no deleterious effects on disease activity.

Key words: Rheumatoid Arthritis, Anaemia, Iron Responsiveness, Ferritin, MCV.

INTRODUCTION

Anaemia in rheumatoid arthritis (RA) is associated with many causes among the gastrointestinal blood loss due to NSAID's (1), deficiencies of vitamin B12 and folic acid (2,3). The anaemia of chronic disease (ACD), originally described by Cartwright (4,5), is a frequent finding in active RA (6,7). Iron deficiency is reported to accompany ACD in RA frequently (8,9). Various theories exist to explain the pathogenesis. Subclinical chronic intestinal blood loss (1), impaired iron absorption (10-12) and a decreased iron release by the mononuclear phagocytic system (MPS) (13-15) are possible explanations, but the findings are equivocal. The most accurate
diagnosis of iron deficiency is made by staining a bone marrow aspirate for iron (16,17), while some parameters can predict iron deficiency like serum ferritin (8,9) and cellular indices (8). Iron deficiency will only be proved by a haemoglobin rise after iron treatment (18,19).

Iron deficiency, however, is considered to be protective in inflammation (20) and infection (21) while exacerbations of disease activity and synovitis (22) have been reported after iron treatment in RA patients.

This study was performed to predict iron responsiveness of anaemia in RA by means of simple erythrocyte and serological parameters, using stainable bone marrow iron as a standard, and to verify whether iron treatment resulted in an increase of disease activity.

**PATIENTS AND METHODS**

**Demographic features**

Twenty-eight patients (5 male), with definite or classical rheumatoid arthritis (23) and a serum haemoglobin (Hb) of less than 7.4 mmol/l, who did not receive iron treatment for at least six weeks previously, entered the study after giving written informed consent. Other causes of anaemia were excluded by history (present or past ulcer disease, other gastrointestinal disease or complaints, hypermenorrhoea and haematuria), negative stools for occult blood, a negative Coomb’s test, a normal vitamin B12, folic acid, creatinin clearance and absence of microscopic haematuria.

Patients were classified according to stainable bone marrow iron content. Group I (no stainable iron), Group II (0-1; normal to very small amount), Group III (2; slight small and patchy content) and Group IV (3 or more; moderate to strong). Groups I and II were considered iron deficient (16,17). The other classification was based on cellular indices (range for MCV 80-90 fl and for MCH 1600-2200 amol). Patients in Group A were hypochromic microcytic, in Group B hypochromic normocytic, in Group C normochromic normocytic, in Group D normochromic microcytic and in Group E hyperchromic macrocytic. Mean age was 64 (48-79) years. A median disease duration of 4 (1-18) years was found, while 71% were seropositive (Rose test) with a mean titer of 261 (reciprocally). 61% percent of the patients received long-acting antirheumatic drugs and 72% used NSAID’s. These data, including age and sex, did not differ significantly in the various subgroups.

**Laboratory procedures**

Haemoglobin (Hb; range 7.4-10.9 mmol/l), hematocrite (Ht; range 0.36-0.59), reticulocytes, mean corpuscular volume (MCV; range 80-90 fl) and mean corpuscular haemoglobin (MCH; range 1600-2200 amol) were measured using route laboratory procedures. (The indices were calculated from haemoglobin, hematocrite and number of erythrocyes).

Serum iron (s-iron) was measured colorimetrically (Instruchemie, Hilversum, The Netherlands; range 14-30 μmol/l). Transferrin was determined with a nephelometer (Ablon Medical Systems, Leusden, The Netherlands; range 44-80 μmol/l). Ferritin was measured by a solid phase enzyme immunoassay (Ferrizyme, by Abbott Labs, Chicago, USA; range 20-150 μg/l).

Parameters of disease activity were erythrocyte sedimentation rate (ESR; range < 10mm/h) measured using the Westergren method, C-reactive protein (CRP) measured by an immunodiffusion technique (Behring Werke, Marburg, West Germany; range < 2mg/l) and C1q binding assay (C1qba) measured by a method originally described by Zubler (24) (range < 3%).

An iron absorption test was performed after an overnight fast. Serum iron was measured before and 2 hours after oral ingestion.