Review

The role of erythropoietin in the anaemia of chronic disease in rheumatoid arthritis

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SUMMARY We reviewed studies on the role of erythropoietin (Epo) in the anaemia of chronic disease (ACD) in rheumatoid arthritis (RA). A relatively impaired Epo response to the anaemia was found in a number of studies although in others serum Epo level was the same as in other types of anaemia. Some arguments are found in favour of a reduced bone marrow-Epo sensitivity although these reflect results mainly from in vitro experiments. It is not yet established whether bone marrow macrophage Epo production is impaired in ACD. In two cases Epo administration to RA patients resulted in increased erythropoiesis. It was concluded that impaired Epo production or reduced bone marrow Epo sensitivity might be associated with ACD but it is not certain whether these factors are causally linked with ACD or side phenomena of RA disease activity. Future Epo treatment in RA and ACD will possibly solve this question.

Key words: Anaemia of Chronic Disease (ACD), Rheumatoid Arthritis (RA), Erythropoietin (Epo), Epo Response, Epo Sensitivity.

INTRODUCTION

Active rheumatoid arthritis (RA) is frequently associated with anaemia (1). Many causes of anaemia in RA are known such as: iron (2,3), vitamin B12 and folic acid deficiency (4,5), adverse reactions of antirheumatic drugs or haemolysis (6,7). Apart from these causes RA is most frequently accompanied by the anaemia of chronic disease (ACD), originally described by Cartwright (8). A vast number of studies have been carried out to examine the pathogenesis of ACD.

Impaired iron absorption (9,10) and decreased iron release by the mononuclear phagocyte system (11) were supposed to play a role but later these findings have been contradicted (12). Ineffective erythropoiesis was found to be a factor in the pathogenesis of ACD (13) although it was also associated with iron deficiency (14). More recent studies focused on interleukins. Interleukin-1 (IL1) (15) and tumour necrosis factor α (16,17) were able to suppress erythropoiesis in vitro whereas their serum levels were raised in ACD, pointing to a potential pathogenetic role in ACD.

Another growth factor, erythropoietin (Epo), has been subject of many investigations. Epo probably has a stimulatory action on erythroid progenitor cells and pronormoblasts (18,19). Its response to the anaemia in
ACD is thought to be impaired, although many findings in these studies are controversial. Here, we review relevant studies on Epo response in ACD and RA in order to establish its role in ACD.

THE ROLE OF EPO IN THE PATHOGENESIS OF ACD IN RA

Serum Epo level

In patients with a normal renal function serum Epo rises after development of anaemia or a hypoxic stimulus (20,21). Possibly Epo has stimulatory effects on the rate limiting enzyme in haem synthesis, delta amino acid synthetase (22). Epo stimulates erythropoiesis in vitro (18,19) and is therefore necessary for in vitro erythroid colony assessment.

Ward (23,24) and Zucker (25) found that serum levels of Epo were low for the degree of anaemia in ACD. Cotes (26) found normal Epo levels in different types of anaemia. Erslev (21,27), in contrast, found higher levels of Epo irrespective of the cause of anaemia. These findings were in agreement with a study by Birgegard (28). He found a negative correlation of Epo with Hb, suggesting a normal response, and with erythrocyte sedimentation rate from which he concluded that RA disease activity determines Epo response and hence Hb. Hochberg (29) confirmed the negative correlation of Epo and Hb while serum Epo was higher in anaemic RA patients.

In other recent studies it was found that serum Epo was higher than in healthy controls but it was the same in RA patients (5,30) without anaemia and with ACD. This suggests that an Epo response is present but it is insufficient to prevent development of ACD. Baer (31) found lower Epo levels in ACD compared to other types of anaemia in RA.

It was shown that serum Epo was higher in iron deficient RA patients than in those with ACD in spite of a comparable Hb level (5,30,31). Epo correlated negatively with serum ferritin (30). These findings suggest a negative correlation between iron stores and serum Epo. It should, however, be realised that iron deficient RA patients in most studies have intermediate levels of disease activity i.e., non-anaemics have a lower level while ACD patients have a higher level of disease activity (3,5,30,31) which might also explain the higher Epo found in iron deficiency. To rule out this phenomenon RA patients with ACD were treated with the oral iron chelator 1,2-dimethyl-3-hydroxypyrid-4-one (30). After 1 week of treatment serum Epo rose, and the rise correlated positively with an Hb rise and ferritin decrease, while RA activity remained unchanged. Therefore, it is not unlikely that increased iron stores in ACD is one of the factors which decrease Epo production.

In conclusion, in patients with RA it seems probable that in ACD Epo response is relatively impaired. Whether or not serum Epo is increased in ACD is not entirely consistent but the rise is not enough to prevent anaemia. Since many other factors are involved in ACD pathogenesis it is not yet established whether impaired Epo response is causally involved in ACD or whether it is a side phenomenon of RA disease activity.

Marrow responsiveness to Epo

If one believes that Epo is one of the major factors in determining ACD it is – in view of the controversies found in serum Epo levels – attractive to speculate on a decrease in marrow Epo responsiveness rather than an insufficient Epo production. Zucker confirmed this for ACD in malignancies (32) but not in ACD in RA (25). However, in vitro experiments might still point to a decreased marrow-Epo responsiveness. It was shown that the number of burst forming units of erythroblasts (BFUe) was reduced in patients with RA and ACD compared to non-anaemic RA patients and healthy controls (17). Harvey also found BFUe numbers to be re-