Iron overload and the risk of bacterial infections in haemodialysis patients. Beneficial effect of erythropoietin

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Introduction

A certain proportion of the dialysis population is transfusion-dependent. As 1 ml of packed red cells brings 1 mg of iron in the body, such patients are prone to develop transfusional iron overload.

The incidence of iron overload in haemodialysis patients is appreciated differently by various authors. Rottelar et al. reported that only 9.5 % of the dialysis population have a ferritin value higher than 1,000 µg/l [1], whereas Hakim et al. reported that as many as 41 % have a ferritin higher than 2,000 µg/l [2]. We found a ferritin higher than 1,000 µg/l in a constant fraction of our dialysis population: between 18 and 20 % over the last 3 years prior to the start of erythropoietin therapy. This more or less corresponds to what Crowley et al. reported: that 15 % of the haemodialysis patients are intensely transfused, requiring more than 10 units of blood per year [3].

Iron overload has been linked to several problems in haemodialysis patients: liver dysfunction, left ventricular dysfunction, endocrine abnormalities, a certain form of osteomalacia, and finally infection [4-6]. What is the available evidence linking iron overload and bacterial infection in haemodialysis patients? What is the mechanism of this association and how to treat iron overload?

Clinical association between iron overload and the incidence of bacteraemia in dialysis patients

Three retrospective studies showed that iron overload in dialysis patients increases the incidence of bacteraemia. We found, in a retrospective study over 6 years, that the incidence of bacteraemia in haemodialysis patients with a serum ferritin higher than 1,000 µg/l was 3.1 times higher than in those with a serum ferritin lower than 500 µg/l [7]. The second study is by Seifert et al. [8], who found that dialysis patients treated with desferrioxamine (DFO) for iron overload and having a median ferritin value of 3,000 µg/l had 3 times more bacteraemia than those treated with DFO for aluminum overload, with a median ferritin of 100 µg/l and than a control group of dialysis patients not treated with DFO, having a median serum ferritin of 200 µg/l. Although these authors could, strictly speaking, not separate the effects of DFO and of iron overload per se on the incidence of bacteraemia, they found an increasing frequency of bacterial infection (not bacteraemia) when patients of the control group, who had never received DFO, were devided according to increasing serum ferritin levels. In a third study, Tielemans et al. found that the annual incidence of bacteraemia in 61 dialysis patients increased as soon as the serum ferritin is higher than 500 µg/l [9]. This increased incidence with higher ferritins was not due to a longer duration of dialysis in patients with higher ferritin values. More recently, we have analysed this relationship in a prospective way [10]. All the 158 patients on haemodialysis in our unit from October 1986 to September 1988 were included in a prospective study during 2 years. All bacteraemic episodes were recorded. Serum ferritin was measured every 3 months by radioimmunoassay and the patients were classified according to their serum ferritin in one of the following categories: ferritin lower than 500, between 500 and 1,000 and higher than 1,000 µg/l. The incidence of bacteraemia was calculated over 181.3 patient-years. We observed a total of 29 bacteraemic episodes, with a yearly incidence of bacteraemia of 0.1173 in the ferritin < 500 µg/l group and a similar incidence (0.1101) in the ferritin 500 to 1,000 µg/l group. In contrast, the yearly incidence of bacteraemia was 0.3404 in the ferritin > 1,000 µg/l group ($p < 0.005$ versus the ferritin < 1,000 µg/l group). When we subdivided the follow-ups according

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to the age of the patients at entry (less or more than 65 years) or according to the duration on dialysis (less than 3 years or more than 3 years), the higher incidence of bacteraemia in the ferritin > 1,000 versus the ferritin < 1,000 µg/l group persisted ($p < 0.005$). This study confirms in a prospective way the results of the 3 previous retrospective studies in showing that when the serum ferritin is higher than 1,000 µg/l, the risk of bacteraemia in haemodialysis patients is approximately 3-fold higher than when it is lower than 1,000 µg/l.

The bacteraemias observed in this prospective study were caused by common micro-organisms, with a well-known preponderance of Gram-positive over Gram-negative bacteria. This association between iron overload and an increased risk of bacterial infection is even more evident for certain micro-organisms, such as particular serotypes of *Yersinia enterocolitica* (0:3 and 0:9). Indeed, dissemination of *Y. enterocolitica* infection usually occurs in patients with iron overload, leading to a so-called 'iron sepsis'. This also applies to the dialysis situation. We reported 10 episodes of *Y. enterocolitica* bacteraemia in haemodialysis patients [11]. Six other reports concern one single patient each [11-14]. Details on iron status and DFO therapy were reported in 14 of these 16 patients, and iron overload was present in all 14. Although some reports mention DFO as playing a predisposing role in the pathogenesis of this infection, the role of DFO in this clinical setting remains unclear, as only 6 out of 14 patients (43 %) were receiving DFO during the development of this generalised infection. Moreover, no dialysis patient has yet been reported to have developed a *Y. enterocolitica* bacteraemia during DFO treatment for aluminum overload in the absence of iron overload. Another bacterial infection which has been associated with iron overload in dialysis patients is *Listeria monocytogenes* bacteraemia [15].

Mechanism of this association

What are the mechanisms underlying the fact that dialysis patients, when iron overloaded, have an increased risk of infection by bacteria in general, and by *Y. enterocolitica* in particular? There are two main explanations. The first one concerns microorganisms, the second one concerns the host's immunity.

During the last decade, the role of iron in the pathogenicity of many bacteria has become more and more evident. The multiplicity of the mechanisms used by microorganisms to obtain iron proves the importance of iron for their survival. Each bacterium has its own way to react to iron starvation: synthesis of siderophores, expression of outer membrane proteins involved in the binding, transport and utilization of iron, ... Likewise, iron-enrichement of the growth medium enhances the growth of many microorganisms [16-18].

The second major reason linking iron overload and infection concerns host defence, particularly the functions of the polymorphonuclear and mononuclear phagocyte [19-22]. In vitro incubation of human granulocytes in a medium containing increasing iron concentrations leads to a progressive decrease in their ability to phagocytose [19]. The deleterious effect of iron overload upon granulocyte function has also been demonstrated in haemodialysis patients. Indeed, Waterlot et al. reported that the ability of the neutrophils from dialysis patients to phagocytose bakers' yeast was inversely related to the logarithm of the serum ferritin value in these patients [23]. We extended this work and compared the ability of neutrophils to phagocytose *Y. enterocolitica* in three groups of subjects: 10 non-uraemic healthy individuals who served as controls, 9 haemodialysis patients who were iron overloaded and 9 haemodialysis patients who were not iron overloaded [24]. Neutrophils from dialysis patients without iron overload had a phagocytosis index of 7.4, similar to that of normals (9.1), whereas neutrophils from iron overloaded dialysis patients had a severely depressed ability to phagocytose Yersinia (phagocytosis index of 1.6). Likewise, neutrophils of these iron overloaded dialysis patients had a killing defect towards this microorganism [18].

Therapy of iron overload in dialysis patients

Once iron overload is present, only 2 therapeutic possibilities exist, if we except phlebotomy: either the chelation of iron with DFO, or therapy with recombinant human erythropoietin.

Desferrioxamine

Does treatment of aluminum- or iron overload with DFO influence the risk of infection in dialysis patients? Bacterial and particular fungal infections have to be considered separately. Does DFO, when given to dialysis patients, affect the incidence of bacteraemia? Three retrospective studies help to answer this question. First, Seifert et al. [8] reported that the incidence of bacteraemia in eight dialysis patients treated with DFO for aluminum overload (median serum ferritin level of 100 µg/l) was no higher than that of 79 dialysis patients who did not receive DFO therapy (median serum ferritin level of 200 µg/l). Second, Chazan et al. [25] reported that the incidence of infection in 18 dialysis patients treated with DFO was not higher than that in 20 patients who were not treated with DFO. Third, we reported a retrospective study in three dialysis centres where 75 patients received DFO

over 73 patient-years, while 217 patients did not receive DFO [26]. The annual incidence of bacteraemia was not significantly affected by DFO treatment, even after stratification according to serum ferritin concentrations. Thus, in dialysis patients, DFO does not increase the risk of bacteraemia, with the possible exception of *Y. enterocolitica* bacteraemia, as discussed previously.

However, DFO selectively increases the risk of mucormycosis caused by fungi belonging to the genus *Rhizopus*. Indeed, since 1986, several reports have described the occurrence of mucormycosis in non-diabetic patients on maintenance haemodialysis. These case reports have recently been reviewed [27-28]. The mechanisms by which DFO could favour a *Rhizopus* infection in DFO-treated dialysis patients are not fully understood. It is likely that the iron-chelate of DFO, ferrioxamine, behaves as a siderophore to *Rhizopus*, increasing iron incorporation and hence promoting fungal growth [29]. The fact that dialysis patients are more prone than non-uraemic patients to develop mucormycosis during DFO therapy could easily be explained by pharmacokinetic changes in dialysis patients, leading to higher ferrioxamine levels [29].

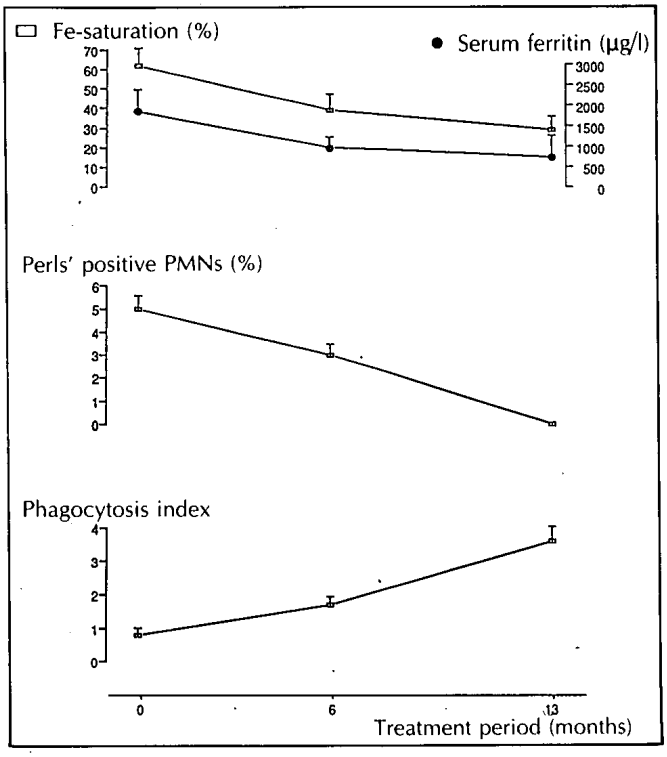

Fig. 1.—Decrease in serum ferritin and iron saturation with time.

Erythropoietin (EPO)

The main objective of EPO therapy in dialysis patients is to improve haematopoiesis. However, the potential of EPO to decrease excessive iron stores in patients with iron overload is also of interest. It their pioneer study, Eschbach et al. reported that during EPO therapy in iron overloaded haemodialysis patients, serum ferritin decreased by approximately 90 µg/l per week of therapy at 150 units/kg three times a week [30]. Subsequently, the same group reported that serum ferritin levels decreased by more than 50 % in 5 iron overloaded patients who received EPO for one year [31]. Eschbach stated that, although iron overload can be corrected, it remains to be learned whether functional derangements in iron-congested organs can be reversed by this form of therapy [31]. More specifically, we wondered whether the granulocyte dysfunction, secondary to iron overload, can reverse during EPO treatment. Preliminary results, obtained in 6 iron overloaded haemodialysis patients treated with EPO during 7 months, showed a significant improvement in the granulocyte index of phagocytosis of *Y.-enterocolitica*, which increased from 0.72 to 1.66 [32]. This study has been extended to 8 patients, 4 of them being followed over 13 months. Figure 1 shows the decrease in serum ferritin and iron saturation with time. At 13 months, stainable iron, as evidenced by the Perls's coloration, could no more be identified in the polymorphonuclear granulocytes. More importantly, the mean index of *Y. enterocolitica* phagocytosis by these cells, when tested in autologous serum, increased 4-fold ($p < 0.01$). This study will be reported elsewhere in more detail (Boelaert JR, Cantinieaux BF, Hariga BF and Fondu PG). Although 13 months of EPO therapy in these patients was not enough to fully normalize the granulocyte dysfunction due to iron overload, this study indicates a likely benefit of EPO to a cell line which is not directly effected by the hormone. If these data can be confirmed in a greater patient group, followed during EPO therapy over a more prolonged period, it is to be expected that the 3-fold increase in incidence of bacteraemia that has been observed in haemodialysis patients with a serum ferritin value greater than 1,000 µg/l, is likely to be reversed [10]. As infection is a major cause of morbidity and the second cause of mortality in this patient population, such a decrease in infection rate would be of great benefit. At present, we are registering prospectively the bacteraemia rate in the hope to validate this prediction.

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