The use of IV iron in the treatment of anaemia of ESRD patients on maintenance haemodialysis: an historical and personal view

Stanley Shaldon

25 Le Michelangelo, 7 Avenue des Papalins, Monaco, 98000

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Dr Schiesser and others have confirmed a well-reported phenomenon, that intravenous (IV) iron in apparently iron-replete patients will decrease the epoetin requirements for a given target haematocrit in patients on maintenance haemodialysis with end-stage renal disease (ESRD) [1]. The original description of a reduction in epoetin requirements by using IV iron in apparently iron-replete patients was first reported in 1993 [2] and the detailed technique of continuous administration of the colloidal iron solution mixed with the heparin solution during the haemodialysis in 1997 [3].

The regular use of colloidal IV iron preparations in the treatment of the anaemia of ESRD patients on maintenance haemodialysis was first reported in 1967 [4,5]. These papers described 53 patients maintained on haemodialysis without blood transfusion. The decision to use IV iron in iron-saturated patients with biopsy-proven haemosiderosis was based upon a single patient observation and merits the use of the term serendipity. The patient was a 42-year-old Swiss alpinist who had received multiple blood transfusions for his anaemia associated with his chronic renal failure between 1962 and 1965. He was referred to the Royal Free Hospital, London with significant hepatosplenomegaly. Liver biopsy confirmed the presence of significant haemosiderosis. After 4 months of training, he was installed on a tank dialysate delivery system and Kiil dialyser in the village of Lauterbrunnen, (visited by Goethe), in the Bernese Oberland in Switzerland. His haematocrit was 24% at the time of leaving London. On return to Switzerland it rose to 38% after several months of dialysis at 1300 m above sea level. The water used for preparation of the tank dialysate was taken straight from the drinking water tap without treatment. He began to experience fever during dialysis and culture of the water revealed a contamination with Escherichia Coli. A water softener was installed and the fevers stopped. The inlet transparent dialysate tubing which had previously been stained with iron deposits became clear and at the same time his haematocrit dropped to 24%. Following this observation, it was decided to give this patient IV iron dextran during dialysis by slow injection during the dialysis with a syringe pump and the haematocrit rose to 48%. A second patient with transfusional haemosiderosis who returned to Amman, Jordan (780 m above sea level) in 1966 had a similar experience with a rise in haematocrit to 40% with the use of IV iron. (Figure 1)

Since that time, I have always used IV iron regularly in all patients on maintenance haemodialysis. After the beginning of the erythropoietin era, IV iron was continued and in 1993 we reported very low erythropoietin requirements in a series of patients on maintenance haemodialysis [2], and the detailed technique of using IV iron mixed with heparin in a syringe was reported in 1997 [3]. The mechanism by which the IV colloidal iron succeeded in raising
the haematocrit without erythropoietin in apparently iron-overloaded patients has never been satisfactorily explained. The terms relative and absolute iron deficiency currently in use seem to be descriptive but not satisfactory. Recent evidence suggests that the blocks in iron transport associated with the old generation of ESRD patients with transfusional haemosiderosis can also be seen in the white cells of ESRD patients who have never been transfused [6]. The conclusion that can be drawn is perhaps that this is a phenomenon of uraemia possibly associated with a chronic inflammatory state [7,8]. The question of what the ideal target haematocrit should be in ESRD patients on maintenance haemodialysis is again under review, as it has been suggested that the haematocrit is not a valid surrogate for survival in patients with ESRD on maintenance haemodialysis [9,10].

The economic savings to health care authorities worldwide in respecting a haemoglobin ceiling of 11.0 g/100 ml should not be underestimated.

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### References

ABO-incompatible transplantation—a safe way to perform renal transplantation?

Jörg Beimler and Martin Zeier

Department of Nephrology, University of Heidelberg, Heidelberg, Germany

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The shortage of donor organs, especially in renal transplantation, leads to an increasing discrepancy between the number of end-stage renal disease patients on waiting lists and the number of available deceased donor kidneys. Expansion of the donor pool can be achieved by increasing the numbers of living kidney transplantation and by overcoming the immunological barriers of ABO-incompatibility and HLA-sensitization. Despite a substantial increase in the number of patients, receiving living kidney transplant, otherwise suitable donors have to be rejected due to pre-existing human leucocyte antigen antibodies or ABO-incompatibility. Isoagglutinins (ABO-antibodies) represent a major barrier in optimizing living kidney donation and organ distribution. As blood group antigens are expressed by the endothelium of solid organs including the kidney, transplantation across the blood group barrier can result in hyperacute antibody-mediated allograft rejection. Depending on blood group distributions in different populations, as much as 30–35% of potential living donors have to be excluded from living donation due to ABO-incompatibility. ABO-incompatible transplantation was already performed as early as in the 1970s, but due to hyperacute rejection, results were discouraging. In 1987, Alexandre et al. [1] published a first series of 26 ABO-incompatible kidney transplantations using splenectomy and an immunosuppressive regimen with steroids, cyclosporine, azathioprine, antithymocyte globulin and donor-specific platelet transfusions. Due to a severe shortage of available deceased donor organs, most ABO-incompatible kidney transplantations have taken place in Japan. Recently published data demonstrated an excellent long-term outcome of ABO-incompatible living donor kidney patients in Japan [2]. Similar successful short-term results have been shown for protocols developed in Europe and the United States. Results from Japan, the United States and Europe are promising, but a lot of questions remain unanswered and there is a lack of standardization among the different protocols. Different approaches to performing successful ABO-incompatible kidney transplantation have been used in different countries over the last decade.

The European way

The recent availability of specific anti-A or anti-B immunoadsorption columns (Glycosorb®) and the use of anti-CD20 monoclonal antibody (rituximab) in different immunosuppressive regimens resulted in the introduction of ABO-incompatible renal transplantation as a routine procedure in different European countries, mainly in Sweden and Germany, including our centre. The first series of ABO-incompatible renal transplantation without splenectomy, using antigen-specific immunoadsorption and rituximab, was published by the Stockholm group of Tyden et al. [3,4]. In 21 patients successfully treated with this protocol, the immunosuppressive regimen consisted of one dose of rituximab (375 mg/m²) given 2–4 weeks...