Benefits and concerns of treating pre-dialysis and renal transplant patients with recombinant human erythropoietin

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Abstract

The possibility of lower efficacy and the fear of increased incidence of side effects may explain the reluctance to use recombinant human erythropoietin (r-HuEPO) in patients with impaired renal function who do not yet require dialysis, as well as in transplanted patients with a failing renal allograft. Several recent studies have clearly shown that r-HuEPO is effective in these patient populations and that the doses needed to control anaemia are comparable with or lower than those needed for dialysis patients. When started at a low dose, the risk of severe hypertension is minimal, although in a significant number of patients intensification of the anti-hypertensive regimen is needed. Moreover, there are no indications that the use of r-HuEPO accelerates the deterioration of residual renal function.

Key words: anaemia; erythropoietin; pre-dialysis; renal transplantation

Introduction

Normochromic, normocytic anaemia is a common problem in patients with impaired renal function. Although the use of recombinant human erythropoietin (r-HuEPO) for the treatment of renal anaemia in haemodialysis and peritoneal dialysis patients is well accepted, its use in patients with impaired renal function who do not yet require dialysis is more controversial. In 1995, after reviewing >200 papers, Muirhead et al. [1] recommended that ‘... for pre-dialysis and failing allograft patients, there is likely little benefit in prescribing r-HuEPO if the glomerular filtration rate is less than 15 ml/min, unless there are compelling clinical indications such as severe angina. The use of r-HuEPO at these low levels of renal function may hasten the development of end-stage renal failure ....’

Factors explaining the reluctance to use r-HuEPO

Several factors may explain the reluctance to use r-HuEPO in pre-dialysis patients and patients with a failing renal allograft. First, it was thought that efficacy may be lower due to the presence of uraemic toxins in patients not yet requiring dialysis. In addition, in patients with a failing allograft, the concomitant use of immunosuppressive drugs could make the bone marrow less responsive, while the inflammatory syndrome associated with chronic graft rejection could also contribute to erythropoietin resistance. Second, there was a fear of severe side effects in patients who do not yet require dialysis, not only in terms of potential aggravation of pre-existing arterial hypertension but also in terms of a more rapid decline of residual renal function. Finally, some concern has been

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expressed regarding cost–benefit in this group of patients.

Over the last few years, several studies have been published that have critically analysed most of the above-mentioned concerns. For the pre-dialysis patients, several prospective controlled trials are available, the three most important being a US study [3], an Austrian study [4], and a study published by Roth et al. in 1994 [5]. For renal transplant patients, the information is more anecdotal, and no prospective controlled studies are available.

As far as efficacy is concerned, the available data indicate that r-HuEPO is certainly as effective in this patient group as it is in dialysis patients. The maintenance doses needed to control anaemia are either comparable with, or lower than, those for dialysis patients. As shown in the Austrian study [4], subcutaneous administration once a week is very effective and is preferable from a practical viewpoint. Also, in renal transplant patients in general, greater doses are not needed [6–9], although in some patients resistance that is probably related to the inflammatory syndrome of chronic rejection can be seen [10].

We can therefore conclude that the concern about lower efficacy of r-HuEPO in pre-dialysis patients and in patients with a renal allograft is not substantiated. However, it must be noted that at least in some transplanted patients the presence of a chronically rejecting graft may induce some degree of erythropoietin resistance.

The fear of severe hypertension when giving r-HuEPO to non-dialysed patients is based mainly on the outcomes seen in the first clinical trials in dialysed patients, in which hypertension was one of the most frequent adverse effects. More recently, hypertension is seen less frequently, mainly thanks to less aggressive dosage schedules. Using these lower starting dosages in pre-dialysis patients, severe hypertension is seen only rarely after starting r-HuEPO therapy. In the Austrian study, no significant alterations in either systolic or diastolic blood pressure were seen after starting r-HuEPO treatment [4]. Likewise, in most other trials, severe hypertension is not a problem if a rapid correction of anaemia is avoided. In many patients, however, there is an increased need for anti-hypertensive drugs. The same holds true for transplanted patients with impaired graft function where an increase in anti-hypertensive treatment is quite often needed [6].

The most important concern with using r-HuEPO in pre-dialysis patients was the possibility of worsening of the residual renal function. This concern was based on the experimental findings in 5/6 nephrectomized rats in which correction of anaemia resulted in an accelerated deterioration of renal function [11]. While anaemia appeared to have a protective effect on glomerular injury, rats treated with r-HuEPO had a significantly greater number of sclerosed glomeruli 4 weeks after ablation. The more severe systemic and glomerular hypertension, however, was the most probable explanation for this accelerated injury. That systemic hypertension played an important role in the pathogenesis of this accelerated glomerular injury was substantiated further by the study of Reudin et al. [12], who showed that control of systemic hypertension could completely prevent the negative effect of correction of anaemia seen in the study of Garcia et al. [11].

Based on an analysis of the slopes of the 1/Scr curve, in neither the US multicentre study [3] nor the Austrian multicentre study [4] could a worsening of residual renal function be demonstrated. In the more recent placebo-controlled study by Roth et al. [5], residual renal function was measured by $^{125}$I-iodothalamate clearance and followed over a period of 1 year. Again, no difference between the r-HuEPO-treated and the control groups could be seen.

Data for patients with a renal allograft are much more anecdotal, and no controlled trial is available at the present time. Again, however, data demonstrating that treatment with r-HuEPO worsens the residual graft function are lacking.

Studies on the socioeconomic consequences and the cost–benefit ratio, as have been done for haemodialysis patients treated with r-HuEPO, are not yet available for pre-dialysis patients. However, all studies have found a significant improvement in clinical condition and quality of life, with an increase in exercise tolerance and work capacity. Studies should also address the question of whether the better overall well-being that results from correcting anaemia may result in postponing the start of renal replacement therapy in some patients.

The use of r-HuEPO and renal transplantation

Soon after the introduction of r-HuEPO into clinical practice, there were suggestions that the higher haematoctrits at the time of transplantation could predispose subsequent renal transplants to graft thrombosis [13] and delayed graft function [14]. More recent studies, however, were not able to substantiate these concerns [15]. According to the data of the Collaborative Transplant Study (CTS), patients treated with r-HuEPO before transplantation are doing at least as well as those not treated with r-HuEPO while on dialysis (G. Opelz, personal communication).

It is difficult to predict whether the more widespread use of r-HuEPO will also diminish the percentage of panel reactive HLA antibodies in highly sensitized dialysis patients awaiting a renal allograft. Only a few studies have addressed this problem, and the results are conflicting [15]. When transfusions stop, some patients also stop making antibodies, while others show persistently high panel reactivity. The ideal solution may, of course, be to avoid blood transfusions completely at the outset. That this approach, which has become more and more popular over recent years, is indeed the best as far as graft outcome is concerned has been challenged once more by the publication of the CTS prospective blood transfusion trial. This showed a significantly better graft survival in patients
who had received at least three pre-transplant blood transfusions than in non-transfused controls [16].

One recent paper by Van Loo et al. also mentioned the use of r-HuEPO to correct anaemia in the post-operative period immediately following transplantation [17]. The authors concluded that r-HuEPO is of benefit in the correction of anaemia during the first few weeks after renal transplantation. However, as could be expected, the haematocrit also increased substantially in the control patients 6 weeks after the operation. Since the number of transfusions in the control group was high, the more relevant question of whether transfusions can be avoided by r-HuEPO cannot be answered. In our own experience over the last 5 years, 79 out of 544 patients (15%) received blood transfusions during the first month after transplantation, with an average of 2.6 units transfused per patient. The average haematocrit at the time of transfusion was 24% [18]. Seventy-three percent of the transfusions were given during the first 2 weeks after transplantation. It is improbable that these transfusions could have been avoided if exogenous r-HuEPO was given to compensate for acute blood loss during surgery.

We conclude that the use of r-HuEPO in pre-dialysis patients and in patients with a failing renal allograft is effective in correcting renal anaemia and that the doses needed to control anaemia are comparable with or lower than those needed for dialysis patients. From a practical point of view, a once-weekly subcutaneous injection is preferable. When started at a low dose, the risk of severe hypertension is minimal, although in a significant number of patients an intensified anti-hypertensive treatment regimen is needed. Finally, there are no indications that the use of r-HuEPO may accelerate the deterioration of residual renal function.

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References