Once-weekly erythropoietic therapy: is there a difference between the available preparations?

Sir,

Iain Macdougall provided, in general, a comprehensive review of once-weekly administrations of epoetin α, epoetin β and darbepoetin α [1]. However, additional mention could have been made of the differences between epoetin α and epoetin β, as well as further analysis of the data from studies of subcutaneous (s.c.) administration.

With regard to the differences between epoetin α and epoetin β, as the article highlights, the validity of once-weekly administration has only been established in large-scale, randomized controlled trials of epoetin β administration [2,3]. Comparable data are not yet available for epoetin α. The results reported by the Swedish Study Group [3] and Locatelli et al. [2] showed that once-weekly epoetin β is an effective regimen in haemodialysis patients in the maintenance phase of treatment. In the Swedish study, the epoetin β dose and haemoglobin level remained stable during the 24-week study, with no statistically significant differences between the groups in change from week 0 to week 24 [3]. The study reported by Locatelli et al. [2] used rigorous and validated statistical methods to show that once-weekly and three-times-weekly s.c. epoetin β administrations are clinically and statistically equivalent. As Macdougall points out, the patients included in these studies were iron replete and well dialysed. However, these inclusion criteria should be regarded as standard in trials of dialysis patients; indeed, they were also adhered to in the two darbepoetin α dialysis studies recently published in full [4,5]. Furthermore, a survey conducted in 2002 of over 2000 haemodialysis patients (~85% of Sweden’s haemodialysis population) showed that ~95% had a Kt/V of >1.0 and 92% and 80% had serum ferritin above 100 and 200 μg/l, respectively (unpublished data, Swedish Society of Nephrology); these values are also in line with current recommendations [6]. Therefore, contrary to Macdougall’s remark about a highly selected, well-dialysed and iron-replete population, the inclusion criteria in the epoetin β trials can be considered representative of the haemodialysis population encountered in clinical practice.

The article also describes results from uncontrolled studies of once-weekly epoetin administration which indicated lack of efficacy. However, patients in the study reported by Jones et al. [7] received both epoetin α and epoetin β. Use of both epoetin products may have contributed to the discrepancy between these results and those reported in the epoetin β randomized trials. This hypothesis is supported by reported differences in the pharmacological properties of epoetin α and epoetin β [8].

Further analysis of data from studies of s.c. administration and its advantages over the intravenous (i.v.) route could also have been provided. For example, with regard to the evaluation of pharmacokinetic profiles, the article only compares the half-lives of i.v. darbepoetin α and i.v. epoetin α (25.3 and 8.5 h, respectively). A comparison should also be made with s.c. epoetin; the reported half-lives of s.c. epoetin α and s.c. epoetin β are 19.4 and 24.2 h, respectively [8]. In addition, s.c. administration gives patients the option to self-administer erythropoietic treatment, and s.c. epoetin has been shown to be more cost-effective than i.v. epoetin [9]. Moreover, in comparison with the i.v. route, s.c. administration may be associated with reduced incidences of erythropoietin-associated hypertension [10]. These benefits, as well as the differences in epoetin α and epoetin β clinical profiles, should be taken into account in an evaluation of erythropoietic therapy.

Conflict of interest statement: I have been involved with clinical trials for Amgen, the makers of darbepoetin (Aranesp®); Johnson and Johnson, the makers of epoetin α (Eprex®); and F. Hoffmann-La Roche, the makers of epoetin β (NeoRecormon®).

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changing the administration route. Scan J Urol Nephrol 1995; 29: 11–14
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Reply

Sir,

I would like to thank Lars Weiss for his interesting comments regarding my Editorial Comment [1] from over a year ago! However, I do have some difficulty accepting one or two of his arguments. While one cannot completely exclude the possibility of different pharmacodynamics between epoetin alfa and epoetin beta, I feel it is unlikely that a difference in intravenous (i.v.) half-life of 6.8±2.7h for i.v. epoetin alfa and 8.8±2.2 h for i.v. epoetin beta, along with 19.4±10.7 h for subcutaneous (s.c.) epoetin alfa and 24.2±11.2 h for s.c. epoetin beta [2] can really make a substantial difference to biological activity. There may be other differences between epoetin alfa and epoetin beta previously unrecognized, but it would be surprising if such subtle differences in pharmacokinetics in a study conducted in healthy volunteers translated into an enhanced clinical efficacy.

However, I do accept completely Weiss’s comment that inclusion criteria including only iron-replete and well-dialysed patients should be ‘regarded as standard in trials of dialysis patients’. As I said in my Editorial Comment [1], and in a follow-up Reply Letter [3], it is always difficult to extrapolate results from scientific studies into everyday clinical practice. While one cannot criticize the inclusion criteria in either the Swedish [4] or Italian [5] studies, the experience of Jones et al. [6] and Geddes and Woo [7] testify to this. I also disagree with Weiss’s comment that a Kt/V of >1 and a ferritin level of >200μg/l are the ‘norm’ in dialysis units; I accept the unpublished data from the Swedish Society of Nephrology, but it is well known that Sweden boasts some of the best results in renal anaemia management in Europe (as reported in the ESAM survey [8]), and the experience in other countries in Europe falls far short of the results that Weiss quotes. Thus, I still feel that we should be cautious about extrapolating results from well-controlled clinical trials into everyday clinical practice in our dialysis units.

Finally, although half-lives aren’t everything, before getting too excited about a possible difference between 19.4 and 24.2 h for s.c. administration of epoetin alfa and epoetin beta, respectively, one should not forget that the half-life for s.c. darbepoetin alfa is substantially greater at 48.8±12.7 h [9].

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The clinical significance of aldosterone in ESRD: Part II

Sir,

We would like to congratulate Epstein for his excellent review of the rapid advances in our understanding of the non-classical effects of aldosterone [1]; however, allow us to add one small word of caution. While the role of aldosterone in endothelial dysfunction is clear and its deleterious effect on survival of patients with cardiovascular disease is undisputed, its clinical significance and effect on survival is not yet demonstrated in patients with end-stage renal disease (ESRD). As recently noted in this Journal, often risk factors for overall and cardiovascular mortality in the general population, such as a high cholesterol [2], obesity [2,3] or hypertension [3,4] are either not found to be risk factors or are paradoxically associated with improved survival. Hyperkalaemia with resulting sustained elevation of aldosterone levels in haemodialysis patients may be an important risk factor in their accelerated atherosclerosis; but perhaps it is not. Over a decade ago, we evaluated the significance of serum aldosterone levels upon non-renal potassium elimination in patients on dialysis. We found a group of patients who were unable to mount an aldosterone response to hyperkalaemia who maintained persistently low levels of aldosterone despite a potassium challenge [5]. Most of the patients in that study are now deceased. When we recently evaluated the data, we found that the effect of the inability to secrete aldosterone appeared not to be protective. Patients with higher aldosterone levels tended to have longer survival (Figure 1).

Although we did not find that the aldosterone level was as significant as dietary restriction in potassium homeostasis, it is possible that some of the benefit may have been due to the aldosterone itself. Of course, there were confounding factors. The patients who were unable to mount an aldosterone response to hyperkalaemia were usually those with hyper-enaemic hypoaldosteronism; who, in turn, were more likely