

Treatment of Anaemia in Dialysis Patients

a report by

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Introduction

Anaemia is a rather frequent complication of chronic kidney disease (CKD). Inadequate synthesis of erythropoietin by the failing kidneys is the main cause, although other factors commonly accompanying CKD, such as iron deficiency, may also be involved. Anaemia often develops early in the course of the disease, considering that approximately one-quarter of patients with only mildly impaired renal function are found to be anaemic.¹ As prevalence of anaemia increases with the progressive decline in renal function, the problem becomes even more important in patients with end-stage renal disease undergoing dialysis. A recent analysis of more than 150,000 patients in the US showed that when starting dialysis 67% and 51% of the patients had a haematocrit below 30% and 28%, respectively.³ In Europe, the results of the Dialysis Outcomes and Practice Patterns Study (DOPPS) – an international prospective survey performed in five different European countries (France, Germany, Italy, Spain and the UK) showed that the overall proportion of prevalent dialysis patients with a haemoglobin level below 11g/dl was of 54% in the period between 1998 and 1999 and of 47% in 2000.⁴

Benefits of Anaemia Correction in Dialysis Patients

The awareness of the importance of treating anaemia in dialysis patients rose from the results of many observational studies showing that such complication has a deeply negative impact not only on quality of life, but on the prognosis of these patients in terms of both mortality and morbidity.^{1,4-7} The reasons for the detrimental effects of anaemia have to be searched for in its primary involvement in the development of left ventricular hypertrophy (LVH), with a role as important as that played by hypertension.^{1,8,9} LVH is very common in CKD patients, with a prevalence that progressively increases along with the decline in renal function,¹ so that up to 70% of incident dialysis patients are affected.¹⁰ In turn, LVH carries a number of detrimental pathophysiologic implications on cardiac function, which ultimately give a major

contribution to increase the burden of cardiovascular morbidity and mortality among dialysis patients.¹¹

In order to effectively counteract the inadequate endogenous production of erythropoietin, research during the 1980s focused on developing a molecule that was equivalent to human erythropoietin through recombinant deoxyribonucleic acid (DNA) technology – the availability of recombinant human erythropoietin (rHu-Epo) for routine clinical use thus became a reality in 1989. The introduction of rHu-Epo in clinical practice actually upset the overall treatment of renal anaemia, previously based upon periodical blood transfusions of the affected patients, and is nowadays reasonably considered as the most significant progress achieved in the field of nephrology, after dialysis was first introduced in the 1960s. There have been several examples of the ability of the rHu-Epo administration to achieve and maintain adequate haemoglobin levels in CKD patients, thus avoiding the need for blood transfusions. Studies performed in dialysis patients showed that higher haemoglobin levels obtained through rHu-Epo administration are associated with a number of benefits for the patients, including improvement of quality of life^{12,13} and at least partial regression of LVH.¹⁴⁻¹⁶

Current Treatment Strategies

Since its introduction in clinical practice, a number of important improvements occurred in the delivery of rHu-Epo therapy, dealing with both the route and the time frequency of administration. Two different rHu-Epo formulations, namely epoetin alpha and beta, have been available for clinical use since the first development of the molecule – they share the same amino-acidic chain of the endogenous hormone, whereas they differ from each other in the glucidic chains, which are linked to the proteic core of the molecule. As to the route of administration, rHu-Epo may be administered either intravenously or subcutaneously, the latter being preferable due to the need for lower dosages, a better pharmacokinetic profile, preservation of vascular vessels and also for practical reasons in CKD patients not receiving haemodialysis. The observation of some cases of pure

red cell aplasia, induced by anti-erythropoietin auto-antibodies in dialysis patients, most of whom were receiving epoetin alpha subcutaneously,¹⁷ led the health authorities of many countries in 2002 to forbid the subcutaneous route of administration for epoetin alpha, but not for epoetin beta, which can therefore still be administered in both ways (subcutaneously and intravenously). The drug is generally administered thrice weekly, although less frequent administrations, such as twice weekly, are used in some cases, particularly in peritoneal dialysis patients.^{18,19} Furthermore, recent studies showed that rHu-Epo given only once a week is as effective as more frequent administrations in keeping the haemoglobin target, ensuring greater compliance by the patient at the same time.^{20,21}

Since 2001, a new molecule, darbepoetin alpha, became available for clinical use – its distinguishing feature is the presence of two additional glucidic chains which make the molecule much more stable in the human body environment. Compared with rHu-Epo, the half-life of darbepoetin alpha is, therefore, prolonged for up to three times when the drug is given intravenously and up to two times when it is administered subcutaneously. As a result, the drug may be administered once a week or once every two weeks, or even less frequently,²² with potential important advantages, both organisational and for the patients.

Open Questions Remain

Despite the satisfying results obtained in the last 15 years through the extensive use of erythropoietin, some matters are still debated, as far as the optimal haemoglobin target to be achieved is concerned. In particular, it is still unclear whether a complete normalisation of haemoglobin levels leads to further advantages compared with only a partial correction, as suggested by current clinical guidelines which recommend to achieve and maintain a target haemoglobin level between 11g/dl and 12g/dl.^{23,24} In a clinical trial, normalisation of haematocrit was found to be associated with greater mortality compared with the partial correction of anaemia,²⁵ but the poor cardiovascular conditions of the patients and the high percentage of grafts as vascular access may have strongly conditioned such results. In another clinical trial performed in patients with less severe cardiac impairment, different haemoglobin targets led to comparable changes in left ventricular parameters, although the degree of LVH regression was found to be correlated with the achieved

haemoglobin level.²⁶ Besides, normalisation of haemoglobin proved to be effective in improving the patients' quality of life and well-being in selected groups of patients, such as younger patients without severe cardiovascular impairment.^{12,13} At the current state of knowledge, therefore, individualising the haemoglobin target, taking into account the demographic features and the co-morbidities of each single patient, is likely to be the strategy able to provide patients with the highest clinical benefit.

Another important question is whether starting anaemia correction at an earlier phase in the course of chronic kidney disease would be more effective in preventing severe cardiovascular damage, which is typically observed in these patients when they start dialysis. To this purpose, convincing answers are still awaited by two on-going studies; the Cardiovascular Reduction Early Anaemia Treatment Epoetin beta (CREATE) and the Anaemia Correction in Diabetes (ACORD). Both of these are randomised, multi-centre, international, clinical trials aimed at evaluating the impact of different haemoglobin targets and different times of starting anaemia correction (on the prevention of cardiovascular complications) in patients with CKD in the conservative phase, as well as on the progression of the disease and on patients' quality of life.^{27,28}

Conclusions

Anaemia is a frequent and early complication of CKD and it is even more remarkable in patients undergoing dialysis. Due to its detrimental effects on the cardiovascular system, firstly by promoting the development of LVH, anaemia has a deep negative impact on a patient's prognosis. The introduction in clinical practice of rHu-Epo, and later of its analogue darbepoetin alpha, revolutionised the treatment of renal anaemia, allowing an effective correction of haemoglobin levels without the need for blood transfusions and, as a result, leading to a significant improvement in quality of life and a global improvement in the clinical status of CKD patients. Nevertheless, some uncertainties as to particular aspects of anaemia management in CKD patients still persist, particularly regarding the time at which anaemia correction should be started and the haemoglobin target that should be achieved. Results from on-going clinical studies are expected to define the modalities of anaemia correction that will allow the achievement of the best clinical results in dialysis patients and, in general, patients with CKD. n

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