Tailored Anaemia Management in Patients with Chronic Kidney Disease

a report by
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The management of renal anaemia in patients with chronic kidney disease (CKD) has been revolutionised by the use of the erythropoiesis-stimulating agents (ESAs) recombinant human erythropoietin (rHuEPO) -α or -β and, more recently, darbepoetin-α. ESAs have been shown to improve quality of life, to lower morbidity and mortality rates, to reduce the need for blood transfusions and to decrease the risk of cardiac complications in pre-dialysis (i.e. patients with CKD stages 3 and 4) and dialysis patients with anaemia.[1]

Following their initial approval, rHuEPO-α and -β were licensed for use three times per week due to their relatively short half-lives (approximately 24 hours when administered subcutaneously (SC)[2]). Because it contains two additional carbohydrate chains compared with rHuEPO, Darbepoetin-α has a three-fold longer terminal serum half-life and greater erythropoietic activity. Its mean terminal half-life is approximately 73 hours following SC administration in peritoneal dialysis and CKD patients.[3-5] Darbepoetin-α can therefore be administered less frequently than rHuEPO while maintaining adequate erythropoiesis. Since the introduction of darbepoetin-α, many physicians have followed less frequent dosing regimens of ESAs, as outlined in the revised *European Best Practice Guidelines*.[1]

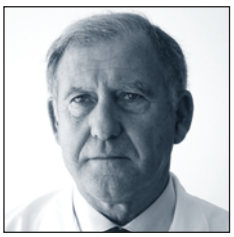
Extended Dosing Intervals with ESAs in CKD

A number of clinical trials have examined extended dosing intervals with ESAs in dialysis (haemo- and peritoneal dialysis) and CKD stages 3 and 4 patients. For darbepoetin-α, these data have established that dialysis patients receiving rHuEPO (three times per week or less frequently) can be switched to weekly (qw) or every-two-week (q2w) intravenous (IV) or SC darbepoetin-α without any increase in total weekly dose.[6-8] A recent study by the author and colleagues reported no significant difference in mean haemoglobin levels or mean weekly dose when CKD patients were switched from qw dosing with darbepoetin-α to q2w dosing and noted that stable haemoglobin levels were effectively maintained with this regimen.[9] Across Europe, rHuEPO is commonly administered by the SC route, thus the ability to switch haemodialysis patients to IV darbepoetin-α without any need for a dose increase has clear advantages for clinical practice. In the chronic renal insufficiency setting, studies have focused on extending intervals well beyond weekly dosing. A number of studies have established SC darbepoetin-α every two weeks for the correction of renal anaemia.[10,11] Furthermore, patients with CKD stages 3 and 4 receiving darbepoetin-α every two weeks were able to maintain haemoglobin (Hb) levels when switched to an extended once-monthly regimen.[12] In Europe, for maintenance therapy once target Hb has been achieved, darbepoetin-α is currently licensed for administration once every two weeks in dialysis patients and once every month in patients with chronic renal insufficiency.[13]

Only a few well-designed studies have assessed the feasibility of weekly rHuEPO dosing in dialysis patients already receiving the drugs twice or three times per week. In most cases, slight decreases in mean Hb levels and/or increases in erythropoietin dosage requirement were observed following the switch.[14,15] In patients with chronic renal insufficiency, once weekly rHuEPO (epoetin-α) increased Hb concentrations in patients not previously receiving ESAs. Similarly epoetin-α once every two weeks, but not once every three weeks, was effective in patients with chronic renal insufficiency already receiving epoetin-α.[16] In Europe, epoetin-α is currently licensed for two or three times per week administration in patients with CKD.[17] Epoetin-β can be administered SC once-weekly or every two weeks in patients (with possible dose increases to maintain Hb stability) already on a stable weekly regimen and only in the maintenance phase of anaemia treatment (i.e. not in patients who are receiving an ESA for initial anaemia correction).[18]

Benefits of Extended Dosing

The ability to extend the dosing interval of ESAs offers clear benefits to patients and healthcare workers alike. For patients with chronic renal insufficiency who often receive their injections at the local doctor's surgery or health centre, less frequent dosing would translate into fewer clinic visits with less overall discomfort. This in turn may improve patient compliance. Nursing time,



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and thereby costs, would be reduced if haemodialysis patients received ESAs on an extended dosing regimen. In addition, fewer injections could reduce the risk of needle stick injuries to both patients and nurses.

Achieving Haemoglobin Stability

Guidelines on the use of ESAs in patients with CKD recommend treating anaemia to a target Hb concentration of above 10 or 11g/dL (depending on the national guidelines for anaemia treatment).[1] Through the use of ESAs as a key component of clinical management, when Hb levels are averaged over a period of time, results indicate that most patients (60–80%) achieve and sustain the target Hb level.[19] In many cases, however, there can be considerable fluctuations in the Hb level underlying these values.

Lack of Hb stability has been shown to be associated with an increased risk of adverse outcomes. Excessively low Hb levels (<11g/dL) are associated with cardiac problems such as left ventricular hypertrophy, heart failure and an increased risk of mortality. In a recent, large retrospective study of haemodialysis patients, the proportion of time patients spent with Hb levels below 11g/dL was compared against the risk of death.[20] There was a clear trend of increased mortality with increasing time below this target; for patients with 80–100% of time at <11g/dL, the risk was approximately 1.8 times as high as for patients with no time below this level. While the consequences of normalised Hb levels are perhaps less clear cut, there is some evidence that, in specific groups of patients, such as those with symptomatic cardiac disease, normalised Hb is associated with increased morbidity and mortality. In a recent report of more than 58,000 patients, Regidor et al. showed the optimal range of Hb to reduce the risk of death in haemodialysis patients to be between 11.5g/dL and 13.5g/dL.[21] In most patients, therefore, tight Hb control is advised and greater Hb stability can be considered an important clinical goal.

Hb stability can be affected by a number of factors such as infection, inflammation or gastrointestinal bleeding. Moreover, patients with CKD tend to have a more variable Hb level than those without. However, adjustment of the ESA dosage is one of the most direct means under the physician's control of maintaining Hb stability. Clearly, a decision on whether to adjust the dosage will depend on the target Hb range that has been predefined by the physician, as well as the current Hb level and an estimate of the direction and rapidity of change. Given the importance of Hb stability in avoiding negative impact on morbidity and survival, it is important to continue to both assess and refine target Hb ranges and to develop a systematic process for deciding by how much and when to adjust ESA dosage. In the last few years, considerable advances have been made in this area through computer-assisted implementation of treatment algorithms.

Computerised Tools

While there are effective ESAs for treating anaemia, clearly the treating clinician's judgements and decisions are critical components of the overall management of individual patients. This is very important when assessing how to maintain the stability of Hb levels. To assist in clinical decisions, and to help standardise clinical management across patients and also across treating centres, computerised decision support systems have been devised and implemented. These leave the ultimate decisions to the clinician, but assist by providing recommendations based on agreed criteria in certain circumstances. Such an approach is particularly helpful in allowing doctors to maximise benefit from evidence-based guidelines. Algorithms for computer-assisted decision support in renal anaemia management have largely been based on guidelines produced by the US National Kidney Foundation or the European Renal Association. Both these guidelines have been produced as a result of rigorous evidence-based analysis of clinical findings. As a consequence, physicians have a basis to treat patients in an objective and systematic manner, rather than simply using personal impressions.

Systems such as those developed in Leeds, UK,[22] have been based on the local hospital laboratory computer records. Here, records of ESA and iron supplement dosage, levels of Hb, serum ferritin and iron status are extracted and analysed against pre-determined thresholds. Recommendations of changes in ESA and iron dosage are then made. This systematic approach is safe, as the limits are within recognised clinical guidelines, and also allows the consistent treatment of large numbers of patients at single or multiple treatment sites. A computer-assisted system has also been used to effectively manage the switching of patients from the older, three-times-weekly treatments to the more convenient qw or q2w regimens of darbepoetin-α.[22]

Such approaches also have the potential of allowing pre-emptive adjustments of treatment before Hb levels diverge markedly from target values, by assessing the rate of change of critical laboratory values. Thus, by making use of agreed target levels and criteria, as well as previous clinical experience in a systematic manner, this should minimise large 'cycling' changes in Hb levels. Computer-assisted decision-making is therefore likely to grow in importance and benefit, and should lead to better and simpler patient management in the future.

Conclusions

Two decades of experience in treating CKD patients' anaemia with ESAs has resulted in an extensive body of clinical practice. The more recent availability of preparations with a longer half-life, such as darbepoetin-α, allows extended dosing intervals, with clear benefits to both patients and healthcare profes-sionals. Guidelines and target values for recommended Hb levels exist. Nowadays, a new concept is being learned – the importance of keeping Hb levels stable in order to optimise anaemia treatment in patients. Recently developed computerised tools can help in achieving this, and in assisting physicians in providing effective and evidence-based care. ■

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