ABSTRACT

Several different erythropoiesis-stimulating agents are now available for the treatment of anaemia in chronic kidney disease. The innovator products (the epoetins) have relatively short half-lives of only a few hours, based on their pharmacokinetic data. Darbepoetin alfa has a more prolonged half-life in vivo, whereas C.E.R.A. has by far the longest half-life of all. The half-life of a drug usually (but not always) impacts on the frequency of dosing. Thus, it is reasonable to suppose that the shorter-acting epoetins have to be administered more frequently than the second- and third-generation agents, and yet studies are available examining the efficacy of all ESAs dosed once-monthly. It seems likely, however, that there is an increasing dose penalty with once-monthly administration of shorter-acting agents, with larger doses required to maintain anaemia correction. At the present time, the evidence for once-monthly administration of C.E.R.A. is stronger than for any of the other currently-licensed ESAs.

Key-Words: Anaemia; C.E.R.A.; darbepoetin alfa; epoetin; kidney disease.

INTRODUCTION

C.E.R.A. (Methoxypolyethylene glycol epoetin beta; MIRCERATM) was licensed in Europe in June 2007. Pharmacokinetic studies convincingly showed that the addition of a polyethylene glycol moiety to epoetin beta greatly prolonged its circulating half-life, to around 130 hours when administered both intravenously and subcutaneously. This compares with around 25 hours for intravenously-administered darbepoetin alfa, 48-70 hours for subcutaneously-administered darbepoetin alfa, 6-8 hours for intravenously-administered epoetins, and around 24 hours for subcutaneously-administered epoetins. The hugely prolonged half-life of C.E.R.A. translates into less frequent dosing, with several studies supporting administration of this agent once-monthly.

At the same time that C.E.R.A. was being developed, several studies appeared in the literature examining once-monthly administration of the epoetins, as well as darbepoetin alfa. While there is little doubt that, in certain selected patients, once-monthly dosing of the shorter-acting ESAs can be achieved, there seems little doubt that this frequency of administration is not appropriate for the vast majority of patients, and that even in those who can be maintained on this frequency of injections, there may be a dose penalty for this.

The aim of this review is to briefly examine the once-monthly (or once-every-4-weeks) studies of the various ESAs, with a view to ascertaining whether all ESAs can be administered once-monthly, or whether C.E.R.A. is the only true once-a-month drug.

STUDIES OF ONCE-MONTHLY EPOETIN ALFA

Two large studies have investigated once-monthly administration of epoetin alfa in anaemic non-dialysis patients.
The PROMPT study, reported by Provenzano et al. examined the administration of subcutaneous epoetin alfa at a total monthly dose of 40,000 units, either administered as 10,000 units every week, 20,000 units every two weeks, 30,000 units every three weeks, or 40,000 units every four weeks. Patients received treatment for a total of 16 weeks, and the primary endpoint for the trial was the mean final Hb measurements of the QW, Q2W, Q3W, and Q4W groups. A total of 519 patients were enrolled; 445 were included in the modified intention-to-treat (MITT) population. The mean final Hb levels of the Q2W and Q4W groups were statistically non-inferior to the QW group. The results of the per-protocol analysis were consistent with the MITT results. In addition, 93.5%, 89.5%, 77.2%, and 76.0% of patients maintained a mean Hb >11.0 g/dl throughout the course of the study in the QW, Q2W, Q3W, and Q4W groups, respectively. The conclusions from this study were that approximately 90% of patients dosed once every two weeks and over 75% of patients dosed once every three or four weeks maintained mean Hb levels >11.0 g/dl.

The second study which is worthy of comment is that by Spinowitz et al. This randomised trial also had four arms with similar but not identical dosing schedules, i.e. 10,000 units QW, 20,000 units Q2W, 20,000 units Q4W, or 40,000 units Q4W for 16 weeks. The primary analysis was a non-inferiority comparison of the 40,000 units Q4W to the 20,000 units Q2W group in the per-protocol population with respect to haemoglobin change from baseline to the end of study. Of the 262 subjects randomised, 229 comprised the per-protocol population. The mean haemoglobin change from baseline for the 40,000 units Q4W group (1.24 g/dl) was not inferior to the 20,000 units Q2W group (1.11 g/dl) with the lower limit of 95% CI, −0.21 g/dl. In the QW, 20,000 units Q2W, 20,000 units Q4W, and 40,000 units Q4W groups, 90%, 87%, 75%, and 86% of subjects, respectively, achieved a haemoglobin increase >1 g/dl. The conclusion from this study was that epoetin alfa can be initiated Q4W in anaemic CKD patients.

Once again, however, these are very high doses of epoetin alfa, which are clearly higher than the average doses required for haemoglobin maintenance with twice- or thrice-weekly dosing of this drug.

Many studies have also examined the administration of darbepoetin alfa once-monthly. Darbepoetin alfa was created as a longer acting erythropoietin analogue. This was achieved by the addition of two extra N-linked carbohydrate chains to the molecule, allowing the maximum number of sialic acid residues to increase from 14 to 22. This conferred greater metabolic stability on the molecule, and increased its elimination half-life from 8.5 hours to 25.3 hours following single-dose intravenous administration, and increasing the half-life from around 24 hours to 48-70 hours following single-dose subcutaneous administration. The drug was developed initially as a once-weekly administration, although many studies showed that once-every-alternate-week dosing was possible with no dose penalty. Several studies attempted to increase the dosing interval even further, out to once-monthly. Thus, Jadoul et al. studied a group of 54 clinically stable haemodialysis and peritoneal dialysis patients who were already receiving Q2W darbepoetin alfa IV or SC. The patients were then switched to once every three weeks (Q3W) dosing for 20 weeks, and if haemoglobin levels remained stable, they could then be switched to once-monthly dosing for another 20 weeks. The route of administration was unchanged. Of the 54 patients who entered the study, 38 patients were deemed stable enough to be converted to darbepoetin alfa administered once-monthly. Of these, 30 patients were able to maintain their target haemoglobin. Thus, for patients who were already stable on once-every-alternate-week dosing, just over half of them were able to be maintained on once-monthly dosing. As with most of the other studies examining once-monthly dosing of
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darbepoetin alfa, this study was uncontrolled, and in selected patients.

A small study by Theodoridis et al.11 showed that haemoglobin levels in 11 peritoneal dialysis patients were maintained following conversion from once-weekly epoetin to once-monthly darbepoetin alfa, although once again the patients in this study were stable, and therefore extrapolation into routine clinical practice may be inappropriate.

Several studies have also investigated the efficacy and safety of once-monthly dosing of darbepoetin alfa to non-dialysis CKD patients12-16. One study examined the administration of darbepoetin alfa in non-dialysis CKD patients not previously receiving an ESA. The proportion of patients achieving a haemoglobin level ≥11g/dL within 100 days was recorded. 80% of patients dosed once-monthly achieved their target haemoglobin, whereas only 50% of those dosed with epoetin alfa once-monthly achieved their target12. Though of interest, these findings need confirmation in a randomised controlled trial before any definite conclusions can be made about once-monthly dosing.

Three studies examined the efficacy of subcutaneous once-monthly darbepoetin alfa in maintaining haemoglobin levels in non-dialysis patients following extension of the dosing interval from once-every-alternate-week dosing13-15. In the study by Disney and colleagues13, 83% of patients who received at least one QM dose of darbepoetin alfa and 95% of the patients who completed the study achieved a target haemoglobin level ≥10g/dL. Likewise, Ling et al.14 reported that the haemoglobin target of 10-12g/dL was achieved in 79% of the modified intention-to-treat population, and in 85% of those patients completing this study following extension of the darbepoetin alfa dosing interval to once-monthly. Finally, the study by Agarwal et al.15 further confirmed the efficacy of once-monthly darbepoetin alfa by showing that following a switch from Q2W darbepoetin alfa dosing, haemoglobin levels could be maintained in the target range in 76% of the modified intention-to-treat population and in 85% of patients who completed the study.

A more recent study was conducted in 152 stable non-dialysis patients from 36 US centres who were already receiving Q2W darbepoetin alfa, and who were then switched to QM darbepoetin alfa16. Patients were stratified according to age (65, 65-74, and ≥75 years). For patients who received at least one dose of darbepoetin alfa, haemoglobin levels were maintained ≥11 g/dL in 76%, 80%, and 71% of patients, while for those who completed the study, the proportions were 83%, 88%, and 85%. Again, it is not clear from this study whether there was a dose penalty in switching patients to QM administration. Unfortunately, this is a limitation of all the above studies in that they are non-randomised and uncontrolled, and thus, it is impossible to make definite conclusions about QM dosing with darbepoetin alfa.

STUDIES OF ONCE-MONTHLY C.E.R.A.

There are now quite a number of randomised controlled trials which have examined the efficacy of once-monthly administration of C.E.R.A. in the maintenance phase of therapy, showing successful maintenance of haemoglobin at this dosing frequency4-7.

Thus, the MAXIMA study4 investigated the potential for IV-administered C.E.R.A. to maintain haemoglobin concentration in haemodialysis patients who were already receiving IV epoetin once- or thrice-weekly. 673 patients were randomised either to continue on IV epoetin (control group), or to receive IV C.E.R.A. every 2 weeks, or to receive IV C.E.R.A. every 4 weeks. Both IV C.E.R.A.-treated groups maintained the haemoglobin in the target range with the same efficacy as the control group receiving IV epoetin, suggesting that IV C.E.R.A. administered once-monthly was effective in managing anaemia in chronic haemodialysis patients4.

The PROTOS study5 employed a similar study design, but with subcutaneously-administered epoetin and C.E.R.A. Thus, 572 haemodialysis patients, who were already receiving SC epoetin once- or thrice-weekly, were randomised either to continue on SC epoetin (control group), or to receive SC C.E.R.A. every 2 weeks, or to receive SC C.E.R.A. every 4 weeks. The conclusions were essentially the same: once-monthly administration of SC C.E.R.A. was effective in maintaining haemoglobin correction in chronic haemodialysis patients5.
In the ARCTOS study, 324 anaemic ESA-naïve non-dialysis patients were initially randomised to receive SC C.E.R.A. Q2W or SC darbepoetin alfa QW. During a second randomisation, the C.E.R.A.-treated patients could either continue on Q2W C.E.R.A. or receive C.E.R.A. once-monthly. The once-monthly C.E.R.A. group maintained correction of anaemia just as effectively as the Q2W C.E.R.A.-treated group or the darbepoetin alfa-treated group, generating further evidence that once-monthly C.E.R.A. was a practical option for the management of CKD anaemia.

More recent post hoc analyses of some of these studies have shown that once-monthly administration of C.E.R.A. maintains a stable haemoglobin irrespective of age, gender, or ethnicity, presence or absence of coronary artery disease or diabetes, and baseline haemoglobin and iron levels. A pooled analysis of four randomised controlled studies suggested that fewer dose changes may be required compared with other ESAs.

Even more recently, data from the PATRONUS study were presented at the World Congress of Nephrology in Milan. This was an open-label prospective randomised controlled trial of once-monthly administration of C.E.R.A. administered intravenously with the same dosing frequency of darbepoetin alfa administered intravenously. It was conducted in a cohort of 490 haemodialysis patients, and to be recruited to this study, patients had to have a stable haemoglobin on once-weekly darbepoetin alfa therapy. They were initially randomised to continue darbepoetin alfa IV every two weeks or C.E.R.A. IV every month for a period of 26 weeks. After this initial treatment period, patients entered a second 26-week treatment period of once-monthly C.E.R.A. and darbepoetin alfa. In both periods, patients were to maintain Hb in the range of 11 to 13 g/dl, with a maximum Hb decrease from baseline of 1 g/dl. The primary endpoint of the study was the response rate for both C.E.R.A. and darbepoetin alfa regimens. Of the total randomised population, 157 patients on C.E.R.A. treatment and 99 patients on darbepoetin alfa met the definition of response (64.1% and 40.4% respectively; P<0.0001). The mean C.E.R.A. dose increased by 6.8% during the second study period (monthly administration), while the mean darbepoetin alfa dose increased by 58.8%. Thus, in this randomised controlled trial, C.E.R.A. maintained target Hb more effectively than darbepoetin alfa at once-monthly dosing intervals, despite large increases in the dose of darbepoetin alfa.

**CONCLUSIONS**

We are now in an era of having short-, medium-, and long-acting ESAs, based on their elimination half-life. Although, in general, long-acting agents can be given less frequently, nevertheless it is possible to give all ESAs once-monthly to stable selected patients. However, there is likely to be a dose penalty for administering short- and medium-acting agents, in that higher doses will be required to achieve the same effect as frequent administration of lower doses of the same ESA. Given current concerns about the potential toxicity of high-dose ESA therapy, nephrologists might do well to avoid stretching the dosing interval beyond what is appropriate for a particular agent. C.E.R.A. is unquestionably the longest-acting agent based on pharmacokinetic data, and evidence for the efficacy of once-monthly C.E.R.A. is accumulating. Although all ESAs correct anaemia and maintain haemoglobin in the majority of CKD patients, it is likely that not all ESAs are the same with regard to their optimum dosing frequency (see Figure 1).

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**ESAs**

| Short-acting | x2 or x3 / week |
| Medium-acting | x1/wk or x1/2wks |
| Long-acting | x1/2wks or x1/month |

**Figure 1**

Schematic representation of dosing frequency in relation to short-, medium-, and long-acting erythropoiesis-stimulating agents.
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