A rationale for an individualized administration frequency of epoetin β: a pharmacological perspective

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Abstract
Several studies have compared the efficacy of once-weekly subcutaneous (s.c.) epoetin treatment with two or three times weekly treatment in renal anaemia. Epoetin administration frequency has attracted a high level of attention in recent years, and numerous small-scale studies have shown comparable efficacy and tolerability of once-weekly vs more frequent administration. The results of two large-scale, randomized, controlled trials of once-weekly administration of epoetin β became available recently. One of these studies, by Locatelli et al., was the first to be designed specifically to demonstrate therapeutic equivalence between once-weekly and three times weekly epoetin β treatment, using rigorous statistical methods. This was a large, multicentre, randomized, parallel group, 24-week study in 173 chronic renal failure patients. Treatment regimens were considered equivalent if: (i) the 90% confidence interval (CI) of the difference between treatment groups was within ±2% for the time-adjusted area under the haematocrit (Hct) curve (AUC); and (ii) for mean weekly epoetin β dose, the 90% CI of the ratio of the groups was between 0.8 and 1.25. As recommended by current guidelines for statistical analysis of clinical trial data, multiple analysis populations were examined in order to demonstrate robustness of the results with regard to the population chosen for analysis. Findings from the primary analysis, the per-protocol population, were confirmed by both the intent-to-treat analysis and an exploratory analysis that examined the influence of five patients who received dose increases above the mean. In all three analyses, the 90% CIs were within the prespecified equivalence ranges for both the difference between treatment groups for Hct AUC and the ratio of mean weekly epoetin β dose. In conclusion, once-weekly and three times weekly s.c. epoetin β treatment regimens are statistically equivalent in terms of maintaining stable Hct levels and dose requirements in haemodialysis patients. The agreement of the three analysis populations provides a convincing demonstration of the robustness of the results. These results confirm that a once-weekly epoetin β regimen is an effective option for management of renal anaemia that may improve patient convenience and compliance.

Keywords: anaemia; end-stage renal disease; epoetin β; equivalence; erythropoietin; haematocrit

Guidelines for management of renal anaemia
Internationally recognized guidelines for patient care are becoming increasingly important in many branches of medicine; indeed, >1000 new guidelines have been produced annually over the past 10 years [1]. Comprehensive guidelines for the management of kidney disease were developed during the late 1990s in both the USA and Europe [2–4], and have become an important reference point for nephrologists. Recombinant human erythropoietin (epoetin) administration is an established treatment for renal anaemia, and its use is extensively covered by the European Best Practice Guidelines (EBPG) and the NKF-DOQI Clinical Practice Guidelines. Both guidelines recommend subcutaneous (s.c.) administration of epoetin, as it is as effective as intravenous administration at maintaining haematocrit (Hct) levels and enables dose reductions of 25–60% [5–9]. The guidelines further advise self-administration wherever possible, reducing the frequency of injections and using administration methods that minimize discomfort, as painful s.c. epoetin injections may affect patient compliance [2,4]. These recommendations will help to improve patient convenience and compliance, as well as reducing workload at nephrology clinics.

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Once-weekly administration of epoetin

Epoetin administration frequency has attracted a high level of attention in recent years, and numerous small-scale studies have shown comparable efficacy and tolerability of once-weekly vs more frequent administration [10–14]. The results of two large-scale, randomized, controlled trials of once-weekly administration of epoetin β became available recently [15,16]. Both studies showed that stable Hct levels can be maintained with once-weekly epoetin β treatment, without a significant increase in dose compared with administration two or three times weekly.

Although both studies confirm the effectiveness of once-weekly administration of epoetin β, there are important methodological differences between them, with each having been designed specifically to answer a different clinical question. The purpose of the study reported by Weiss et al. was to detect any differences in efficacy between different administration frequencies of epoetin β [15]. In contrast, the study by Locatelli et al. was designed to demonstrate therapeutic and statistical equivalence between administration regimens [16]. This latter study was the first to address specifically the issue of equivalence of different administration frequencies of epoetin β, and used rigorous, validated pharmacological and statistical methods suitable for this purpose.

The results of this study have been reported previously [16], focusing mainly on analyses of the per-protocol patient population. This paper expands upon these results, comparing and discussing results from the per-protocol and intent-to-treat (ITT) analyses and an exploratory analysis.

Therapeutic equivalence of once- and three times weekly epoetin β

The methodology of this study has been reported in detail previously [16]. In brief, this was an open-label, randomized, parallel group study, conducted over 24 weeks in patients with chronic renal failure (CRF) on regular dialysis treatment, who received either once- or three times weekly s.c. epoetin β (Figure 1). The primary efficacy variables were Hct values [assessed according to the time-adjusted area under the curve (AUC)] and mean weekly epoetin β dose (IU/kg body weight).

The primary variables were analysed using an analysis of covariance (ANCOVA) model. The two treatment regimens were considered to be equivalent if both (i) for the Hct time-adjusted AUC, the 90% confidence interval (CI) of the difference between treatment groups was within ±2%; and (ii) for mean weekly epoetin β dose, the 90% CI of the ratio of the groups was between 0.8 and 1.25. The pre-specified range of ±2% for the Hct AUC was chosen to reflect the usual target range for Hct in renal anaemia (30–35%), whilst the 0.8–1.25 range selected for epoetin β dose is often used in bioequivalence studies [17].

The ITT population included 163 patients (81 in the once-weekly group and 82 in the three times weekly group), and 134 patients were included in the per-protocol analysis (69 in the once-weekly group and 65 in the three times weekly group). The exploratory analysis (n = 65 and n = 64 in the once- and three times weekly groups, respectively) examined the influence of four patients in the once-weekly group and one patient in the three times weekly group who received dose increases of >200%.

Treatment was well tolerated and mean Hct values remained stable throughout the 24-week follow-up period in both treatment groups [16]. The difference between the two groups for the mean time-adjusted AUC for Hct was −0.54% according to the per-protocol analysis, −0.56% according to the ITT analysis and −0.19% according to the exploratory analysis. The 90% CIs for these values were within the pre-specified range of −2 to +2% (Figure 2).

The ratio of the two groups for mean weekly epoetin β dose was 1.11, 1.05 and 1.04 according to the per-protocol, ITT and exploratory analyses, respectively. The 90% CIs for all analyses were within the pre-specified equivalence range of 0.8–1.25 (Figure 3). The fact that the CIs for both variables (Hct AUC and mean weekly epoetin β dose) fell within the pre-specified ranges for equivalence demonstrated that the two treatment regimens are statistically equivalent.
The three data sets analysed in this study all supported the conclusion of statistical equivalence of once- vs three times weekly administration of epoetin β.

Different analysis sets play different roles in the analysis of clinical data. Guidelines for statistical analysis of clinical trials recommend that, in general, alternative data sets should be analysed in order to demonstrate a lack of sensitivity of the results to the choice of population for analysis [18,19].

The ITT analysis is generally recommended as the primary analysis in trials designed to demonstrate superiority of one treatment over another [18,19]. Inclusion of patients who violate the study protocol or fail to complete trial medication, as in the ITT population, will tend to reduce the estimated treatment effect, as true treatment benefits may be masked. If results are statistically significant despite this apparent reduction, the analysis is strongly supportive of a genuine difference between treatments.

In contrast, the ITT analysis is not considered to be conservative in equivalence trials. Recent guidelines indicate that per-protocol analyses are the statistical methodologies most likely to detect an effect of treatment in equivalence trials [18,19]. However, when ITT and per-protocol analyses arrive at the same conclusions, as in this study, the results are considered more robust [18,19].

Guidelines also recommend investigation of the influence of outlying data, where this can be justified both medically and statistically, via an analysis reducing or removing the outlier effect [18,19]. In this study, the exploratory analysis revealed that the observed group ratio of 1.11 for mean weekly epoetin β dose in the per-protocol population was due to the effect of four patients in the once-weekly group and one patient in the three times weekly group who had received large dose increases towards the end of the study. Several factors, including iron deficiency, concomitant medications and diseases, and resistance to epoetin treatment, may be considered in order to explain these dose increases. In at least two of these patients (both from the once-weekly group), concomitant diseases of hyperparathyroidism, gastritis and alcoholic liver cirrhosis are likely to have contributed to the increase in dose.

The agreement of the three data sets indicates the robustness of the results and provides a convincing demonstration of equivalence between once-weekly and three times weekly epoetin β administration frequencies. Furthermore, these data confirm the results of previous studies suggesting the effectiveness of once-weekly epoetin treatment [10–15].

Conclusions

This study was the first to be designed specifically to demonstrate statistical equivalence between once- and three times weekly s.c. administration of epoetin β, using rigorous statistical methods. Per-protocol analyses are recommended for equivalence trials; however, as highlighted by guidelines for analysis of clinical trial data, conclusions can be regarded as more robust when established in more than one analysis population.

Three analysis populations were considered in this study. For both the ITT and per-protocol analyses, the CIs for the difference between the two groups for the Hct AUC and the ratio of mean weekly epoetin β dose fell within the pre-specified equivalence ranges. This finding was confirmed further in the exploratory analysis that examined the effect of four patients in the once-weekly group and one patient in the three times weekly group who received dose increases above the mean. The agreement of all three analyses provides a compelling argument that once-weekly epoetin β treatment is statistically equivalent to three times weekly administration in maintaining stable Hct values, confirming similar findings by previous authors.

The availability of a once-weekly s.c. administration frequency, and the use of a multidose vial formulation
that allows versatility in terms of dose individualization, could reduce demands on clinic and nursing time. Also, for many patients, the option of once weekly administration may encourage them to self-administer treatment, potentially improving convenience and compliance. Once-weekly treatment with s.c. epoetin $\beta$ is consistent with the current trend towards encouraging self-administration [2–4], and this will be assisted further by devices designed to facilitate self-administration.

In conclusion, this study uses rigorous, validated methodologies to demonstrate statistical equivalence of once-weekly and three times weekly epoetin $\beta$ in maintaining anaemia correction. The results confirm that a once-weekly epoetin $\beta$ regimen is an effective option for long-term management of anaemia in patients with chronic kidney disease.

References