Hemoglobin targets: the jury is still out

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Much has been made recently of the results of the CREATE [Drüke et al. 2006] and CHOIR [Singh et al. 2006] studies which, together with the findings of a meta-analysis of nine randomized, controlled clinical trials [Phrommintikul et al. 2007], have indicated that the setting of higher hemoglobin (Hb) target concentrations in patients with chronic kidney disease (CKD) actually increases mortality [Strippoli et al. 2007]. While these studies have provided us with much to consider, we would like to discuss a number of issues arising from these analyses which mean that the position is not yet definitively resolved and that any verdict on the clinical utility of treatment to achieve Hb targets must await the results of further, robustly designed, large-scale clinical trials.

The limitations of meta-analyses are already well documented, and further critical review finds a number of limitations of the analysis by Phrommintikul et al. [2007]. In particular, although the meta-analysis found that patients with a higher target Hb had an increased risk of all-cause mortality and arteriovenous access thrombosis than those randomized to groups with lower target Hb, both findings were dominated by data from the US Normal Hematocrit trial [Besarab et al. 1998], which contributed 58% and 75% of the weight, respectively. Unlike the other studies, inclusion criteria for this trial were congestive heart failure or ischemic heart disease, meaning that patients were already at high cardiac risk [Macdougall and Ritz 1998].

A recent critique of the CREATE and CHOIR studies raised a number of important issues concerning their design and conduct and, consequently, the validity and applicability of their findings [Levin 2007]. Notable issues for the CHOIR study are its open-label design with the potential for bias in the study’s conduct, and the high withdrawal rate – 38% of patients did not complete the trial and no reasons for discontinuation were cited for over half of them. Moreover, the analysis did not include all randomized patients, excluding those who had not experienced any event at termination. With regard to the findings of the study, it is not unreasonable to question whether the statistically significant differences between the two treatment groups in the baseline incidences of coronary artery bypass grafting and hypertension could have impacted on the differences in outcomes seen. Further, the failure to achieve Hb targets in a high proportion of patients, despite the administration of unusually high mean epoetin alfa doses in the two groups (median doses of 11,000 units), suggests that the patients were in a worse disease state on entering the study than is usual for a CKD population. Thus, while the conclusions drawn by the CHOIR investigators might indeed be appropriate for the patient population in that study, the flaws in its conduct and data analysis mean they cannot be extrapolated to the wider CKD population. A more appropriate summary of the CHOIR study findings might be that the data indicate that patients with significant cardiovascular disease who require high doses of erythropoiesis-stimulating agents (ESAs) to achieve target Hb levels may not be helped by ESA therapy targeting a normal Hb level. It is notable that the CHOIR study was stopped after an interim analysis for presumed futility (the inability to show a benefit in the higher Hb target group) rather than any concrete evidence of harm to patients.

Analysis of the CREATE study similarly exposes a number of problems with its design and conduct. The open-label design again introduced the risk of bias in this study, such as the unintentional selection of healthier pa-
tients to enroll due to concerns over cardio-
vascular disease. Another prominent issue is
that the study protocol did not stipulate when
to initiate dialysis. A greater number of pa-
tients in the higher Hb target (13.5 g/dl) group
went on to receive dialysis; however, the
open-label design may have resulted in a de-
lay in initiating dialysis in patients in the
lower (11.5 g/dl) Hb target group because
their symptoms were wrongly attributed to
anemia rather than uremia. The most signifi-
cant issue with the CREATE study, however,
is that the observed annual event rate of 6% for
the composite cardiovascular disease end-
point was much lower than the expected 15%,
so that the study was underpowered to demon-
strate any difference between the treatment
groups. Nevertheless, the study did not demon-
strate harm to the patients randomized to
the higher Hb target group and, in keeping
with most other studies, patients’ general
health and physical function improved signif-
ically in the higher Hb target group com-
pared with the lower Hb group.

In summary, while recent papers have
provided nephrologists with much food for
thought and have sounded an important cau-
tionary note, questions regarding the benefits
and risks of treatment to correct anemia in
CKD patients – and of the optimal target Hb
level – remain to be answered by further
large, randomized, controlled trials. One such
trial, the TREAT study, is ongoing and the
Data and Safety Monitoring Committee have,
following careful consideration, found “no
cogent evidence to recommend its alteration
or termination” [Pfeffer 2007]. We would ad-
vocate that it is still too early for a verdict to
be reached on this matter, and that the jury
should remain out, pending this and other ran-
donized controlled trials.

Acknowledgment

The authors would like to acknowledge
editorial support provided by Gardiner-
Caldwell Communications Ltd.

Conflict of interest

Dr. Carrera is scientific consultant, mem-
ber of steering committees for international
clinical trials and/or member of international
advisory boards for the following companies:
Amen (Europe), Roche (International) and
Shire (International).

Dr. Macdougall has received research
grants, honoraria and lecture fees from
Amen, Ortho Biotech, Roche, Shire and
Affymax.

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