Conflict of interest statement. None declared.

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Reply

Sir,

We thank Ergün and Keven for their response and constructive remarks. We agree that diet and lifestyle intervention should generally be recommended for patients with new-onset diabetes mellitus after transplantation. However, in this study, the patients were treated within a few weeks to 6 months after transplantation at a time when an weight restriction may not be appropriate. Furthermore, the intention with our study was to examine the safety and efficacy of rosiglitazone given to patients receiving relatively high-dose triple immunosuppression. Although these patients were not very hyperglycaemic (three had impaired glucose tolerance and seven had mild diabetes), the treatment appeared safe and effective as evident from oral glucose tolerance testing. HbA1c, glycohaemoglobin, was measured before and after rosiglitazone treatment. However, the treatment course was not long enough to improve HbA1c. Monitoring fructosamine would have been a good idea to assess these short-term effects, but the analysis is unfortunately not clinical practice in our hospital. We agree that tacrolimus may be more diabetogenic than cyclosporin. Only three recipients received tacrolimus in our study, which makes it inappropriate to apply statistical tests. Actually, at this early stage after transplantation, prednisolone dose seems to be a major critical determinant for new-onset diabetes and impaired glucose tolerance [1]. Insulin resistance is particularly pronounced at this early stage after transplantation and, thus, an insulin sensitizer might be a sound treatment option [2].

In the Guidelines there is an assumption that iron dextran preparations can be considered as a single class of product and as such the recommendations are dismissive of all iron dextran formulations. Closer scrutiny of recent published literature would reveal that low molecular weight iron dextran offers a safety profile that is very different from the older high molecular weight iron dextran complexes [1–6]. Low M.W. iron dextran has a significantly lower risk of both serious and non-serious acute adverse drug events compared to high M.W. iron dextran [1–6].

In the same issue of *Nephrology Dialysis Transplantation*, in which the Guidelines were published, Chertow *et al.* evaluates all reported adverse drug events recorded by the FDA during three years (1998–2000), where a total of 21 million doses of 100 mg iron were administered. The study reports a superior safety profile for low molecular weight iron dextran (INFeD®/CosmoFer®) vs the high molecular weight iron dextran (Dexflow®). The study also reveals that the rates for total ADEs are significantly lower among those patients receiving low molecular weight iron dextran than those receiving iron gluconate.

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Sir,

Evidence-based Guidelines provide a valuable framework for developing and implementing treatment strategies for patients. As such they should be based on a comprehensive search and appraisal of prevailing evidence. We write to express concerns regarding the omission of evidence relative to the above mentioned section.

The Guidelines recommend the use of iron sucrose and iron gluconate over iron dextran. The bibliography indicates that newer studies documenting the differences in regard to safety between high and low M.W. iron dextran were not considered. Neither did the drafting of the Guidelines include recent documentation concerning the acute toxicological profiles of the available parenteral iron formulations or issues associated with long term safety.

Revised European Best Practice Guidelines for the management of anaemia in patients with chronic renal failure, part III.2: treatment of anaemia with iron

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Studies that specifically address serious or life-threatening adverse events suggest that they are rare in patients administered low molecular weight iron dextran [1,3]. The largest prospective studies on the safety of parenteral iron are not comparative, so it is unclear as to whether these rare serious ADEs are less common with one particular parenteral iron than with other forms of intravenous iron. We suggest that the paucity of evidence (especially comparative) makes it inappropriate to indicate which may be the safest IV iron preparation.

Traditionally a safety analysis of pharmaceutical products considers both the short and long term safety aspects covering typically acute adverse drug events and the potential long term consequence of the toxicological profile. We suggest that in preparing the next revision of the European Guidelines a comprehensive analysis should be conducted in regard to the difference between the toxicological profiles of the currently available parenteral iron formulations. We draw your attention to recent studies that focus on long term safety concerns associated with the loosely bound iron complexes, iron sucrose and iron gluconate. These studies relate to free/labile iron and oxidative stress and cytotoxicity which are considered clinically important and therefore influence the choice of parenteral iron.

Zager et al. (2004) [7]:

"Parenteral iron formulations have potent, but highly variable, cytotoxic potentials which appear to parallel degrees of cell iron uptake: (iron sucrose > iron gluconate << low M.W. iron dextran)"

Agarwal et al. (2004) [8]:

"The data in humans confirm the suggestion of Zager et al. that there was direct renal injury with injected iron sucrose."

The European Best Practice Guidelines should also consider that low M.W. iron dextran administered as total dose infusion (TDI) is the only real treatment option for iron deficient predialysis patients, home hemodialysis, or PD patients, since weekly visits may be unrealistic. This is also the recommendation in the K-DOQI guidelines.

In conclusion, we request that the evidence relating to both the short and the long term safety profile of currently available parenteral iron compounds is appraised and considered in a revision of the European Best Practice Guidelines and the K-DOQI Guidelines. We especially urge the appointed guideline committee to acknowledge and review the safety literature regarding low M.W. iron dextran (CosmoFer®/INFeD®), which will ensure that they have embraced all current parenteral iron supplement options, and add credibility and support to such a publication.

Conflict of interest statement. None declared.

Nebo a/s Odd Vaage-Nilsen President Roervangsvej 30 DK 4300 Holbaek Denmark Email: rie.greve@pharmacosmos.com

Reply

Sirs,

We appreciate the comments by Dr Vaage-Nilsen on the section on Iron Management from the recently revised European Best Practice Guidelines for the Management of Anaemia in Patients with Chronic Renal Failure. In fact, they highlight two of the problems with the creation of clinical practice guidelines in general.

The first problem relates to what evidence to include and what to exclude in formulating such guidelines. Dr Vaage-Nilsen alleges that we omitted evidence in relation to this section, and also that some of the newer studies in relation to high and low molecular weight iron dextran were not considered. As the Methodology section from the revised EBPG indicates, a very comprehensive literature search involving over 5000 abstracts was initially conducted, and although much of this evidence did not end up being included in the Guidelines bibliography, this was only after a thorough assessment and scrutinisation of the quality of evidence available to support the various recommendations. Thus, some evidence was indeed omitted, but it is incorrect to assume that the evidence was not considered.

The Working Group for the Guidelines was aware of the recent publications suggesting differences in the safety profile between the older high and the newer low molecular weight iron dextran complexes [1,2], and although these studies are of interest, the data were considered to be preliminary and not strong enough to justify a recommendation to use low molecular weight iron dextran at the present time. True anaphylactic reactions to intravenous iron compounds only occur with iron dextran due to preformed dextran antibodies; these antibodies do not cross-react with iron sucrose or iron gluconate, and no such antibodies have been detected against sucrose or gluconate. Thus, there is a physiological justification for having concern about severe life-threatening reactions to iron dextran, but not iron sucrose or iron gluconate. It may be (but is still not yet proven) that the incidence of these severe reactions is less with the lower rather than the high molecular weight dextran complex, but even with the low M.W. iron dextran they still occur. In the report by Fishbane et al. [3], 27 patients (4.7%) had adverse reactions that were related to the low molecular weight iron dextran. In addition, four of these patients (0.7%) had reactions that were classified as serious (one cardiac arrest; three hospitalisations). Ten patients (1.7%) had reactions that were classified as anaphylactoid.

Vaage-Nilsen also makes reference to the paper by Chertow et al. [4]. As he acknowledges, this paper was published in the same issue of this Journal as the Guidelines were published, and thus was not available to the EBPG Working Group. However, data reported in this paper suggest that reactions to even the low molecular weight iron dextran can be fatal (9 deaths reported by Chertow et al. [4]). Thirty one deaths due to iron dextran were also reported by Faich and Strobos [5]. In the paper by Chertow et al. [4], which Nebo generously supported, the authors analyse