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Reply

Sir,

We would like to thank Dr Hirschberg and colleagues for their interest in our report, which was aimed to raise awareness of the rare but repeatedly described untoward effects of deferoxamine on renal function. Moreover, we aimed to propose a mechanism by which these untoward effects on renal function could be mediated [2]. In the discussion we stated that a different drug, deferasirox, has 'been repeatedly shown to cause acute renal failure' quoting a recent paper by Kontoghiorghes [3]. Dr Hirschberg and colleagues, who, as members of the renal safety board for deferasirox, had detailed knowledge of the post-marketing surveillance data, are 'very sceptical' that deferasiox was responsible for these cases of acute renal failure.

We can only refer to data available in the public domain. According to the FDA website, there had been 115 reports of suspected adverse drug reactions in the association with the use of deferasirox from 2 November 2005 to 20 June 2006 (http://www.fda.gov/cder/dsn/2007_fall/nme.htm). Sixteen unduplicated reports described renal adverse events. Seven patients improved after discontinuation of deferasirox. Seven patients had 'acute renal failure' with an onset between 5 and 58 days after initiation of the therapy. Dr Hirschberg and colleagues state that 'the term acute renal failure was inappropriately used in many cases to describe a relatively minor increase in serum creatinine ($<2\times$ upper limit of normal) that developed over the course of several weeks'. Unfortunately, there had been no uniformly accepted definition of acute renal failure [4]. However, in a variety of settings, there is accumulating evidence that small increments in serum creatinine are associated with adverse outcomes [4]. Therefore, the term acute kidney injury (increase of creatinine >25 μmol/l over 48 h), which is often superimposed on pre-existing CKD, was recently introduced. This definition will increase the clinical awareness and the detection of injury to the kidney and should, in our view, also be used in the setting of pharmacovigilance. Aside from the FDA information, Vichinsky *et al*. [5] showed in 132 adult and paediatric patients that deferasirox administration was accompanied in a mild and stable increase of serum creatinine in 36.4% of the patients. Of the 63 patients in that study that received deferoxamine, 22.2% experienced such an increase of serum creatinine. In contrast to deferoxamine, where the mean change in creatinine was 3.06 μmol/l, the mean increase in the deferasirox-treated group was 6.3 μmol/l. Unfortunately, serum creatinine only rises after a substantial loss of glomerular filtration rate and is also influenced by many factors like gender, weight and race. Estimation of glomerular filtration rate, e.g. by measuring cystatin C, would therefore be the preferred way to monitor renal function. Data on proteinuria, another important marker of renal damage, are missing completely.

As vividly illustrated by the post-marketing information of Novartis on deferasirox (14 May 2007), a pro-active approach to *potential*, even rare side effects of new drugs are in the best interest of the public. A uniform assessment of renal function and renal injury, e.g. by determination of estimated GFR and proteinuria, as proposed in a science advisory of the AHA for the assessment of patients with or at increased risk for cardiovascular disease [1], would provide a better scientific basis for the monitoring of untoward renal effects of new drugs.

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HDF promise for the future

Sir,

The February issue of *Nephrology Dialysis Transplantation* amply reported on online haemodiafiltration (HDF) as a possible promise for the future [1].

Please note the following erratum in Table 1 of the Editorial Comment, concerning our study with reference 16: high-volume HDF in postdilution was compared with

high-flux *haemodialysis* (*hf*HD) with regard to the removal of beta2-microglobulin (b2M) and not with low-flux HD (*lf*HD), as is reported.

Although most studies with online HDF demonstrate a higher removal of a broad range of the molecular spectrum of uraemic compounds versus HD, confusion still persists on the preferred method of HDF. With regard to the location of inflow of the substitution fluid, most studies rely on post-, pre-, mid- or mixed dilution, but this results in different removal rates. It is regrettable that in several references in the Editorial Comment, even the used HDF method was not mentioned (Table 1). Yet this is essential for the knowledge of the efficiency of the treatment. For instance, it is well known that with high-volume predilution HDF, a lower clearance of small molecules is achieved versus high-flux HD. Besides, a lower b2M clearance is noted in high-volume predilution HDF, compared with postdilution HDF with the same amount of substitution volume (80 ml/min) [2]. In view of these results, it is not surprising that in the ongoing trials in the Netherlands and France high-volume HDF in postdilution is chosen.

It is also stated in the Editorial Comment that conflicting results concerning phosphate clearance were reported. When comparing phosphate removal with high-volume (100 ml/min) HDF in postdilution, our group observed a 19% higher removal versus high-flux HD [3].

Finally—as in our department, routine high-volume postdilution HDF is performed since 1993—in dialysis patients with more than 10 years of treatment, a lower prevalence of carpal tunnel syndrome is reported in reference 16 of the Editorial Comment. Concerning survival, recently our group reported a 26% survival benefit [4], comparable with the data of the DOPPS study and of the observational study from Eastern Europe.

Conflict of interest statement. None declared.

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Reply

Sir,

We thank Lornoy and De Meester for their relevant comments on our recent article [1] and their correct erratum concerning the applied membranes in reference 16 (Table 1).

Indeed, the location of the inflow of substitution fluid in haemodiafiltration (HDF) is of considerable relevance in terms of determining the efficacy of small and middle molecular weight clearance. Therefore, it is regrettable that in many of the referenced papers in the Comment (references 9, 32, 33, 41 and 43), the method of HDF is not explicitly mentioned. This lack of information is particularly present in the large observational studies on mortality. So, besides the general shortcoming of observational studies, i.e. the risk of selection bias, also the different methods of HDF could have resulted in an even greater heterogeneity in design of the studies.

Currently, more and more data on mortality rates during HDF are being presented. Apart from De Meester *et al*., who reported a 26% survival benefit for HDF (De Meester *et al*. *ASN Renal Week* 2007, abstract SA-PO494), a Portuguese group presented their data during the 2007 ASN meeting as well (Natario *et al*. *ASN Renal Week* 2007, abstract SU-PO559). They observed in a single-center cohort of 88 haemodialysis (HD) and HDF patients during almost 2 years of follow-up and after adjusting for baseline characteristics and comorbid conditions, a 79% decrease in mortality risk.

Recently, a 22% reduction in all-cause mortality in patients on HDF was found in a prospective observational study performed in 757 prevalent patients in Italy [2]. No difference in all-cause mortality was seen in patients on HDF using bags and online HDF. However, cardiovascular mortality was lower in patients on online HDF as compared to HDF using bags and to conventional HD. Regrettably, again the technique of HDF (pre- or postdilution) was not described in the method section.

All together, these observations underscore the need for properly designed and conducted randomized clinical trials on the effect of HDF on all-cause and CV mortality. We hope that the Dutch CONvective TRAnsport STudy (CONTRAST), in which online postdilution HDF is applied and compared to standard HD, will be such a study [3]. With the results of CONTRAST, and other comparable studies [4,5], we hope that the promising results of the large, observational studies on HDF can be confirmed. Only then can HDF be considered no longer a ‘promise for the future’, but instead an accepted treatment in terms of evidence-based medicine.

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