Letter and Reply

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Could Pentoxifylline (PTX) be a promising agent to reduce the systemic inflammation in hemodialysis patients?

Sir,
González-Espinoza et al. [1] reported that pentoxifylline (PTX) progressively and significantly reduced serum levels of tumor necrosis factor-α, interleukin-6 and C-reactive protein in the hemodialysis (HD) patients. They further concluded that PTX could be a promising agent to reduce the systemic inflammation in patients with end-stage renal disease on HD. However, we have concerns about those interpretations.

First, the reduced serum level of inflammation markers should not be attributed exclusively to PTX. Two other factors may also be contributing to this. (i) The baseline values of inflammation markers may be a factor. In HD patients without any clinical interference, higher initial values are often followed with a deceasing trend, lower ones with an increasing trend [2]. Therefore, with significantly higher initial baseline values in the PTX group, the reported decrease in inflammation markers might simply reflect this beginning bias. (ii) The effect of dialysis adequacy may also be a factor. In HD patients, when the dialysis is adequate, the impaired function of monocytes tends to improve, indicated by the increased level of cytokines [3]. When dialysis is not adequate, the functions of monocytes are less likely to recover, which further leads to a decreased level of inflammation markers. In González-Espinoza’s paper, the value of equilibrated Kt/Vurea was significantly higher in the control group. Also, the values of serum urea and creatinine were lower than those in the PTX-treated group. The subjects in the PTX-treated group may not have dialysis adequacy.

Second, the reduced levels of inflammation markers may not indicate improved inflammation in HD patients. When the inflammation is improved in HD patients, the response to erythropoietin treatment increases with a higher level of hemoglobin [4]. However, in González-Espinoza’s paper, the Hb value decreased with the values of inflammation markers also decreasing.

Considering the initial inequality between the placebo and PTX group and the contradicting finding about Hb, a more conservative conclusion would be better.

Conflict of interest statement. None declared.

References

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Reply

Sir,
The phenomenon that Ji et al. are talking about has been largely known in statistics as ‘regression toward the mean’ [1]: when a value of a variable is extreme on a first measurement, it will tend to be closer to the mean on a second measurement. However, this is hardly probable to occur in our study because we used several strategies to counteract this phenomenon [2]: a clinical trial design, the use of a control group and measurement of inflammation markers at three different time points. We did not have ‘extreme’ median values in any of the measurements, and importantly, ‘similar patterns’ were observed in the three studied inflammation markers (it would be uncommon to obtain values considered as regression to the mean in three markers!). Additionally, statistical analysis of inflammation markers was performed with repeated measurement analysis of variance on ranks (not only with before–after tests).

The Meuwese’s paper [3] that you are referring to cannot be considered a study of natural course because it
was not designed for this purpose (it does not describe the use of anti-inflammatory drugs, for example). In fact, what this paper shows is that four patterns of inflammation can be found in hemodialysis patients during follow-up—stable-low, decrease, increase and stable-high—, and that persistent elevation and increases of C-reactive protein, interleukin-6 and tumor necrosis factor (TNF)-α over a short period of time is associated with a worse outcome.

Your statement about inadequate dialysis in the pentoxifylline (PTX) group is a little bit confusing. Even though the control group had higher equilibrated Kt/Varea than PTX group, both groups had values considered as adequate [4]. Supposing, without accepting, that PTX patients had inadequate dialysis, according to your statement, this group would have higher inflammation than controls throughout the study; however, patients in the PTX group decreased all the studied inflammatory markers, whereas they remained roughly the same or increased in the controls (without changes of dialysis dose in both groups throughout the follow-up). Moreover, one has to be cautious extrapolating data from in vitro studies to in vivo situations; the study that you are referring to [5] was performed in vitro and only measured IL-12p70.

Finally, as you stated, PTX has been shown to increase values of hemoglobin by means of decreasing TNF-α values; however, this is not the only factor influencing hemoglobin levels in patients on hemodialysis [6]. These latter factors may have influenced hemoglobin values in our study, and more importantly, as we recognized in the discussion, this issue cannot be appropriately evaluated as erythropoietin dose was not controlled by researchers, and its use is still a matter with local economical implications.

All these issues were appropriately considered and discussed in the paper; therefore, the conclusions are sustained.

Conflict of interest statement. None declared.

References

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Immunostaining findings in IgA nephropathy: correlation with histology and clinical outcome in the Oxford Classification patient cohort

Sir,
I have read with interest the article by Bellur et al. [1] published recently in your premier journal. It describes the immunohistological findings of IgA nephropathy (IgAN) and their correlation with the clinical and histological features of this disease at the time of renal biopsy and the final renal outcome. The study cohort used for this study is the same as that used for the development of original Oxford Classification of IgAN. The study may be considered as an important adjunct to the original Oxford Classification of IgAN, which was entirely based on the pathological evaluation of morphological features [2, 3]. It is worth mentioning here that soon after its publication, some investigators raised the point of lack of immunofluorescence (IF) or electron microscopic (EM) findings in the original classification and their correlation, if any, with the morphological and clinical features at the time of diagnosis and the final outcome [4].

In the backdrop of the above facts, the study is certainly welcome addition to the Oxford Classification of IgAN. However, there is one caveat. The subject study is entirely based on careful scrutiny of the original renal biopsy reports and not on the re-examination of the archived frozen renal biopsy material by the IF test. I have the experience of working on one such project nearly 2 years ago at the Pathology Department of Academic Medical Center (AMC), Amsterdam, under the supervision of Prof. Sanderine Florquin and Dr. Joris Roelofs, which involved repeat IF study of the archived frozen tissue of all IgAN cases in AMC Pathology Department files (M. Mubarak, unpublished data). As I have first hand experience of working on this subject, I have a couple of points to make about this study, the clarification of which will be helpful for all the renal pathologists in their routine practice as well as future research projects on this subject. The points are as follows:

(1) As we all know, the interpretation of capillary wall IF positivity is quite subjective and shows marked interobserver variability. It is worth reiterating here that I have not come across a single case of IgAN with the IF findings similar to those shown in Figure 1B of the subject study. On the other hand, the majority of cases showed peripheral capillary positivity of IgA as shown in Figure 1A. Obviously, the question arises of the definition of capillary wall positivity of IgA staining here. For that matter, do the authors recommend using an immunohistochemical approach for determining the accurate capillary wall positivity?