Steroids and Cytotoxic Drugs in the Treatment of Membranous Glomerulopathy

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Dear Sir,

We offer the following comments to the critiques of Dr. Ponticelli and Dr. Wardle on our editorial 'What Is the Basis for the Use of Steroids in the Treatment of Membranous Nephropathy?'

The main points raised by Dr. Ponticelli are (1) that the long-term natural course of membranous nephropathy (MN) is not benign and (2) that assessing the prognosis of MN by the renal survival rate at 2 years is misleading. Both statements have been challenged by recent data. The conclusion that MN has not a benign long-term prognosis derives from the review [1] of retrospective studies published more than 10 years ago and mostly obtained in a limited number of patients [2–4]. In the most recent series patients' survival at 10 years ranges from 75 to 92.5% [5–10] with percentages of kidney loss not exceeding 8–10% [6, 7]. Possibly better supportive measures (i.e. dietary manipulation, the appropriate use of diuretics, antihypertensive agents,...) may have contributed to change the natural course of MN in the last years. These considerations together with the notion that MN presents mostly in a relatively old age range raise the question of the benefit/risk ratio of exposing this patient population to high-dose steroids and chlorambucil. A low percentage of patients with MN indeed have a poor prognosis and progress to terminal renal failure [5]. However, as documented by the recent study of Donadio et al. [5], in the majority of these patients renal failure develops within 2.5 years after the initial diagnosis. This is why assessing the renal survival rate at 2 years is meaningful. It has also to be pointed out that only data of 2 years' follow-up were available from the two major studies [11, 12] considered at the time our Editorial was written. Now the results of other two trials are available which seriously question the overall efficacy of steroids and chlorambucil in MN. In a controlled trial performed in the United Kingdom, which started 7 years ago and has been just completed, the same steroid schedule as that utilized by the American Collaborative Study Group [11] failed to reduce proteinuria or to improve disease progression in MN [13]. The efficacy of alternated courses of steroids and chlorambucil, as proposed by Dr. Ponticelli, has recently been addressed by other investigators [14] who have been unable to document at least from the preliminary analysis of the data, any significant therapeutic effect of this regimen in patients with MN. One can argue that in the above-mentioned studies data were analyzed after a mean follow-up of 36.6 + 17.2 months which contrasts with the longer follow-up of the study by Ponticelli et al. [12] (41.3 ± 19.8). However, 26 out of 32 patients given steroids and chlorambucil in that study had complete or partial remission within 31.4 months again in sharp

contrast with the data of the study by Vosnides et al. [14] who, in the same period of time, observed a reduction in proteinuria in 2 out of 14 patients given steroids and chlorambucil as well as in 2 out of 11 on no treatment. As far as the comments of Dr. Wardle are concerned it is very difficult to understand the main point of his critique. Probably, we can easily add to the list he had made 10 or more biochemical effects of anti-inflammatory steroids but the fact these agents exert an action on enzymes, chemical mediators, and immunocompetent cells is not synonymous of a therapeutic effect, i.e. a net benefit for the patient. Pharmacokinetics may be 'boring' but are not 'useless', because it is impossible in modern medicine to establish an effective dose and a correct schedule of treatment without taking into consideration also the concentrations of drugs in blood and tissues. We remain therefore of the opinion that an effort should be made to improve our understanding of the mechanism of action of steroids and that high doses of glucocorticoids and other potentially harmful drugs should not be utilized for the routine treatment of a disease such as the MN showing a relatively benign course in the majority of patients.

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