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Editorial

IgA nephropathy: What patients are at risk of progression to end-stage renal disease and how should they be treated?☆

Nefropatía IgA: ¿qué pacientes están en riesgo de progresar a enfermedad renal terminal y cómo deberían ser tratados?

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Introduction

There is general agreement that the basic treatment of IgA nephropathy (IgAN) consists in the renin–angiotensin–aldosterone system blokade (RAASB) in patients with proteinuria >0.5–1 g/day or hypertension.[1] Randomized controlled trials (RCT) have shown significantly better renal survival in patients on such a therapy, for as long as the goals of proteinuria and blood pressure are achieved.[1–4] By contrast, the usefulness of steroids and other immunosuppressive drugs is today a controversial topic.

Although the KDIGO guidelines on the management of glomerular diseases indicated a cycle of steroids in patients who maintain proteinuria >1 μg/day despite an optimized RAASB,[1] the subsequent publication of the STOP-IgA5 study has raised many doubts about the usefulness of immunosuppression in this disease. In this review, we present recent data on the profile of patients with IgAN at risk of progression and we propose some ideas that, in our opinion, may help decision-making in this difficult matter.

Hematuria in IgA nephropathy: the grand forgotten

According to the KDIGO guidelines, the risk of progression to end-stage renal disease (ESRD) of a patient with IgAN is determined by the mean proteinuria during follow-up, glomerular filtration rate and blood pressure.[1] Although there are no prospective studies, the influence of proteinuria on the rate of progression has been verified in retrospective studies with

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a large number of patients and with a prolonged follow-up.[6,7] These studies show that an average proteinuria greater than 0.5–1 g/24 h was associated with a poor renal prognosis.[7]

In contrast to the central role of proteinuria, little attention has been paid to hematuria as a factor of poor prognosis in IgAN, even though it is a cardinal clinical feature in this entity. Outbreaks of macroscopic hematuria are a typical onset of the disease and microscopic hematuria between outbreaks is observed in the vast majority of patients. Outbreaks of macroscopic hematuria can precipitate an acute renal failure due mainly to tubular damage caused by the hemoglobin released by the red blood cells in the tubular lumen.[8,9] Elderly patients are more susceptible to the deleterious effect of these outbreaks, especially when they have chronic renal failure. In addition, a correlation has been described between the duration of the hematuria outbreak, the severity of the renal failure and the recovery of renal function after a given outbreak.[9] Those interested in the clinical characteristics and the pathogenesis of acute renal failure induced by hematuria are recommended to read recent reviews on the subject.[10,11]

The influence of outbreaks of macroscopic hematuria in the prognosis of IgAN has been extensively discussed and is a controversial issue. Some authors have even proposed a favorable influence on long-term renal prognosis,[12] but this observation is probably biased by the fact that outbreaks are more frequent in children in the early stages of the disease. On the contrary, more recent studies by our group indicate that outbreaks, especially those of prolonged duration, frequently have a devastating effect on adult and elderly subjects with IgAN.[9,13]

But, as opposed to the macrohematuria outbreaks, very few studies have analyzed the prognostic relevance of microhematuria in IgAN. This lack of interest is striking, since, as we have stated before, it is a distinctive finding of this entity and its evolution is very different from some patients to others. In some patients the amount of microhematuria tends to decrease and eventually disappears after a variable period of time. The disappearance of hematuria, accompanied by a proteinuria <0.2 mcg/day and stable renal function, is defined as clinical remission of the disease and can be achieved spontaneously or after immunosuppressive treatment. The number of patients with spontaneous remission is not known with precision, although it is probably related to the aggressiveness of the clinical presentation. Thus, in the GLOSEN study that analyzed the long-term evolution of patients who started with moderate proteinuria (0.5 g/day), glomerular filtration >60 ml/min/1.73 m^2 and microhematuria, spontaneous remission was observed in 37% and the long-term prognosis was excellent.[14] Other patients present microhematuria of variable intensity that may be persistent or intermittent.

The few studies that have analyzed the prognostic influence of microhematuria have serious limitations. These are, a short time of follow-up, the evaluation of the urine sediment in a some point in the time (at the beginning of the disease or at some isolated occasion throughout the follow-up) or the quantification of the hematuria by dipstick and not by analysis of the urinary sediment with a microscope. Probably because of these limitations, the results of these studies are contradictory and the conclusion are not solid.

Our group has published recently[15] an exhaustive analysis of the prognostic influence of the amount of hematuria in a cohort of 112 patients with IgAN followed through an average of 14 years and which has been considered as the first consistent approach to this problem.[16] The strength of the study lies mainly in the prolonged and regular follow up of the patients, with systematic determination of urinary sediment in each visit. Patients were divided according to the amount of mean proteinuria during the follow-up (time-averaged proteinuria [TA-P]) in 2 groups: TA-P > 0.75 g/day and TA-P < 0.75 g/day, and according to the mean amount of hematuria during follow-up (time-averaged hematuria [TA-H]) in those with persistent hematuria (average H-HR, 24 red blood cells per field) or minimal or negative hematuria (TA-H average 0.2 red cells per field). We observed that the percentage of cases that developed ESRD or reduced their renal function by at least 50% during follow-up was significantly greater in cases with persistent hematuria (30% and 37%, respectively) than in those with minimal or negative hematuria (10 and 15%, respectively). The multivariate analysis showed that TA-H, TA-P, baseline renal function and the presence of tubulo-interstitial fibrosis in the biopsy were independent predictors of ESRD. In those patients in whom the hematuria disappeared throughout the follow-up (46% of the patients), the rate of reduction of renal function went from -6.45 ± 14.66 to -0.18 ± 2.56 ml/min/1.73 m^2/year after the disappearance of the hematuria.

In our study, we also confirmed that the renal survival of patients with an average proteinuria >0.75 g/day was significantly worse than that of subjects with proteinuria below than this value. However, when we analyzed the evolution of patients according to the combined mean amount of proteinuria and hematuria during follow-up, we observed that those with mean proteinuria >0.75 g/day and persistent microhematuria (18% of the total, 21/112 cases) had a significantly worse renal survival than the other groups of patients (persistent proteinuria without haematuria, persistent hematuria without significant proteinuria or clinical remission). Among these 3 groups the renal survival was similar. Of the 21 patients with sustained proteinuria and hematuria, 11 (52%) developed ESRD and 12 (57%) had a loss of renal function >50%, as compared with 11% and 16%, respectively, in the remaining patients. Another interesting finding was that 8 of these 21 cases received different types of immunosuppressive treatments with a significant reduction of proteinuria and hematuria and the loss of renal function was attenuated. But, the small number of patients prevented drawing conclusions in this regard.[15]

In summary, this work confirms an impression that many clinical nephrologists have had: that patients with IgAN and significant proteinuria (>0.75 or >1 g/day) present a stable clinical course when the sediment is negative. This observation is particularly relevant if we take into account that the indication of immunosuppressants (mainly steroids) has traditionally been based on the persistence of proteinuria above these ranges despite the optimization of RAASB, without taking into account the findings of urinary sediment.[1,4] By contrast, our data indicate that immunosuppression therapy should be reserved for those cases with proteinuria >0.75–1 g/day that also present an active sediment, with significant microhematuria (>15–25 red cells per field) that is persistent.[15]