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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]

Should histological lesions be taken into consideration to decide immunosuppression therapy?

The Oxford classification was an important advance to improve our prognostic capacity in the IgAN. After an exemplary international collaboration, 4 histological lesions were identified that independently predict the deterioration of renal function (loss of 50% of the function renal or ERT).[17–19] These lesions are mesangial hypercellularity (M0 or M1, depending on the absence or presence of mesangial hypercellularity in >50% of the glomeruli), endocapillar hypercellularity (E0 or E1, absence or presence of any degree of endocapillar hypercellularity), segmental glomerulosclerosis (S0 or S1, absence or presence of some glomerulosclerotic lesion) and tubular atrophy/interstitial fibrosis (T), which graduates according to the severity of interstitial fibrosis (T0: 1–25%; T1: 26–50%; T2: >50%).

On the basis of this classification, the MEST score has been coined, whose prognostic capacity has been validated in several international studies.[17–20] These studies show that the addition of the MEST score to the classic risk factors for progression (proteinuria, glomerular filtration, blood pressure) improves the predictive capacity.[19] Other studies[21] have evaluated the influence of immunosuppressive treatments on the predictive capacity of MEST, or the prediction of response to these treatments based on histological lesions. In a subanalysis of the international cohort VALIGA, it was observed that the patients showing the best response to steroids were those with mesangial and endocapillary proliferation, glomerulosclerosis and tubulo-interstitial fibrosis.[21]

More recent studies have confirmed, using a similar methodology, the prognostic influence of the presence of crescents. This has led to a modification of the MEST score that includes the number of crescents, the MEST-C (for "crescents"): C0: no crescents, C1 crescents in less than 25% of glomeruli and C2, in more than 25%.[17]

Despite the very important accumulated evidence about the value of MEST lesions, it must be emphasized that it is based on retrospective studies. A definitive confirmation should be made by performing RCT in stratifying patients according to the MEST-C score. In any case, given the solidity of the aforementioned retrospective studies, we believe that there is sufficient basis to consider the MEST-C score (along with the aforementioned clinical factors: proteinuria, blood pressure, glomerular filtration and haematuria) when evaluating an immunosuppressive therapy in patients with IgAN.

Complement and IgA nephropathy

Considerable evidence has been accumulated in recent years about the participation of the complement system in the pathogenesis of NIgA. Data show the participation of the lectin pathway in the pathogenesis of the disease,[22] the regulatory effect of factor H on the activity of the alternative pathway seems to be compromised by a frequently observed elevation in serum levels of FHR1 and FHR5.[23,24] The deletion in the genes encoding these proteins FHR1 and FHR3 is associated with a lower risk to develop the disease.[25]

All data point to a deregulation of the complement with important implications in the progression of the disease. In addition to the therapeutic possibilities that are starting to be proposed, these anomalies may help to differentiate early in the disease those patients with a greater risk of progression and, therefore, susceptible to more specific approaches than the simple RAASB. Thus, a multi-center work of GLOSEN[26] showed in a series of 283 biopsies of patients with IgAN, that 109 of them (38.5%) had glomerular deposits of C4d and that their renal survival at 20 years (28%) was significantly worse than that of the C4d negative patients (85%). Similar results were obtained in another recent Spanish study[27] showing that the presence of glomerular C4d in patients with normal renal function independently and significantly predicts a worse subsequent evolution of the disease.

Steroids, mycophenolate and other immunosuppressive treatments in IgA nephropathy: an overview

A thorough review of immunosuppressive treatment in NIgA is beyond the scope of this manuscript, so we will limit our review to the aspects that we consider most important. Regarding steroids, several RCT showed a favorable effect in subjects with proteinuria >1 g/day and glomerular filtration >50 ml/min/1.73 m^2.[28,29] These data led the KDIGO guidelines to recommend a cycle of 6 months of steroids in patients who maintained proteinuria >1 g/day after a period of at least 6 months of optimized RAASB.[1] However, the guide emphasized the weaknesses of these studies: a high percentage of patients had not been treated with RAASB and in other cases the RAASB was suspended before randomization. Subsequent to the publication of the KDIGO, a retrospective study, which analyzed a large number of patients through propensity score matching, showed a favorable effect of the steroids. Interestingly, the beneficial effect was more clear r in subjects with higher degrees of proteinuria and with filtrates lower than 50 ml/min/1.73 m^2.[21]

Two recent RCTs have been able to solve some deficiencies of previous studies, especially the small number of patients and the lack of rigorous design. However, their results still do not clarify the role of immunosuppression in IgAN. In the STOP-IgA,[5] 309 cases with proteinuria >0.75 μg/day were included in a 6-month period of optimized RAASB. In one third of cases, proteinuria was satisfactorily controlled with these measures. The remaining 2/3, who maintained proteinuria >0.75 ng/day in spite of the BSRAA, were randomized to continue only with supportive treatment or to add immunosuppression (steroids if the glomerular filtration rate was >60 ml/min/1.73 m^2 and steroids + cyclophosphamide/azathioprine if it was <60 ml/min/1.73 m^2). Although the number of patients who achieved complete remission was higher in those who received immunosuppression, there was no difference in the loss of renal function during the 3 years of the study and complications (diabetes, overweight, infections) were more frequent in immunosuppressed patients.

The TESTING study,[30] planned to include more than 700 patients with proteinuria >1 g/day and varying degrees of renal function, was stopped prematurely because the rate of adverse effects, especially infections, was significantly higher in patients treated with prednisone (0.6–0.8 mg/kg/for 2 months) ($n = 136$) than in those who received placebo ($n = 126$). Despite this, the number of renal events (ERT, renal cause death, 40% reduction in GFR) was significantly lower in patients treated with prednisone.

Taken together, we dare to summarize the available evidence by stating that steroids seem to be effective in IgAN, but in many cases the adverse effects outweigh the possible benefits in the kidney. In this scenario, it seems decisive the search for other immunosuppressants that would allow the discontinuation or at least reduction of the dose of steroids. In this regard, no additional benefits have been obtained with cyclophosphamide, azathioprine, or rituximab, tested more recently.[31]

The use of mycophenolate (MF) in IgAN deserves a more detailed comment. Although the KDIGO guidelines did not recommend its use based on 2 RCT that did not show obvious favorable effects,[1] in other subsequent studies an antiproteinuric effect was observed in the treated group[32] and, with longer follow-ups, this rendered an improvement in renal survival.[33] More recently, another RCT (176 patients) compared high and low doses prednisone, adding MF to the group of low doses of steroids; the rate of complete remissions was similar in both groups (an estimated figure of 48% and 53% respectively at 12 months), but the number of side effects was, as expected, lower in the group of MF.[34]

Interestingly, a marked improvement in histological lesions was observed in some patients who were rebiopsied. The histological improvement induced by MF has also been highlighted in another recent study[35] that, although without a control group, performed an additional second biopsy in 18 patients who had received MF as monotherapy for a mean of 28 months. A significant improvement of the endocapillary and crescent hypercellularity was observed as compared with the first biopsy.

These latest data indicate that in IgAN the use of MF can help to reduce steroids or may even be effective as monotherapy. Based on these data, our group decided to treat with a prednisone regimen (0.8–1 mg/kg/day as starting dose, with a rapid reduction at low maintenance doses) plus MMF 1.5–2 g/day or its equivalent in sodium MF for 12–18 months to patients with a risk profile. The first 13 treated patients had significant proteinuria despite RAASB, a sediment with intense microhematuria and a glomerular filtration rate of 43 ± 11 ml/min/1.73 m^2. After treatment, we observed a significant reduction in proteinuria (from 2.5 ± 2.6 to 0.7 ± 0.7 g/day, $p = 0.002$), a decrease or even rapid disappearance of hematuria and a change in the rate of loss of renal function, from -35 ± 14 ml/min/year to $+2 \pm 4$ ml/min/year; $p = 0.001$) (unpublished data). And, the treatment was well tolerated.

Obviously, these possible favorable effects of low-dose steroids plus MF need to be validated with well-designed RCTs. But it is important to note that in all studies conducted to date the patient selection has been based solely on the criterion of proteinuria. This limitation also affects another recently published RCT,[36] which demonstrated the administration of an enteric budesonide, designed to be released at the level of the distal ileum (a zone rich in Peyer's plaques, where theoretically large amounts of abnormal IgA are synthesized in patients with IgAN), significantly decreased proteinuria and stabilized renal function compared to the placebo group. Studies already underway are aiming to confirm this important therapeutic alternative.

Although immunosuppression may have a favorable effect in cases with evident deterioration of renal function,[21] it is important to bear in mind the "point of no return" in IgAN, that is, the degree of parenchymal kidney damage that makes it highly unlikely that any intensive treatment will be able to prolong renal survival. There is no precise definition of this term, some authors use values of serum creatinine higher than 2.5 mg/dl or glomerular filtration rate lower than 30–50 ml/min/1.73 m^2.[4] However, It should be emphasized that clinical expression of IgAN may start with acute renal failure, and in other patients it is observed a rapid deterioration of renal function, associated with inflammatory and proliferative kidney lesions that may respond to immunosuppression.[21] Therefore, to use certain level of renal failure to define the "point of no return", it is essential to consider that such a deterioration of kidney function has been reached for a long time (years), that is, chronic rather that acute deterioration of renal function. It is reasonable to think that the presence of lesions of advanced glomerulosclerosis or extensive tubulointerstitial fibrosis in a recent biopsy reinforces the definition of "no return" in a specific patient, but in general it is not necessary to perform a renal biopsy, except in cases in which there is a lack of information about previous evolution.

Key points

- The presence of persistent and significant microhematuria should be added to the traditional criterion of proteinuria >0.75–1 g/day despite optimized RAASB, to select patients candidates for immunosuppressive treatments. Accelerated loss of renal function, together with the above criteria, reinforces the indication of such treatments.
- From the previous point there are patients that should not receive immunosuppressive treatments. These are patients with creatinine >2.5 mg/dl or a glomerular filtration rate <30–50 ml/min/1.73 m^2 documented in recent years, or cases with extensive tubular interstitial and advanced glomerulosclerosis in renal biopsy ("point of no return" in IgAN).
- The information provided by the renal biopsy (MEST-C score, deposit of C4d in the immunofluorescence) should be used, in conjunction with the clinical criteria, for early identification of patients susceptible of treatment.
- With all the limitations above mentioned, today, the combination of low-dose steroids plus MF seems to be the most reasonable immunosuppressive treatment.

– To confirm the usefulness of immunosuppressive treatments and new therapeutic possibilities (enteric budesonide, complement blockers), we need well-designed studies, which include patients with sustained proteinuria and hematuria and who also take into account the aforementioned histological data.

Conflicts of interest

The authors have no conflicts of interest to declare.

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