For over 20 years, randomized controlled trials have studied the use of immunosuppression in patients with IgA nephropathy (IgAN). While studies agree on the effectiveness of corticosteroids, doubts still remain concerning other immunosuppressants [1–4]. Even the KDIGO guidelines recommend the use of renin–angiotensin system (RAS) blockers and corticosteroids.

Data from the STOP-IgAN study showed that, after 36 months, corticosteroids are effective in reducing proteinuria, but not in preserving renal function [5]. Why this contradiction? For some years, it has been highlighted that time-average proteinuria (TAp) is the best predictor of renal survival in IgAN patients. However, no difference in renal survival was found at TAp values of up to 2 g/day in the first 24–36 months, whereas differences became apparent after longer follow-up, i.e. the lower the TAp, the better the renal survival [6–9]. Unfortunately, in the STOP-IgAN study, the limited follow-up period of 36 months does not allow assessment of renal survival using proteinuria as a parameter. But how did proteinuria itself perform in the STOP-IgAN study? During the 6-month run-in phase, proteinuria level decreased in all patients. However, following randomization, there was no further reduction in proteinuria level in the supportive care group, suggesting that the maximal effect of RAS blockers on proteinuria had occurred in the first 3–6 months. In contrast, the supportive care plus immunosuppression group showed a further sharp proteinuria decline after randomization, at least in the first 6 months. Subsequently, proteinuria level increased again, although this did not occur in all patients in the supportive care plus immunosuppression group, since those treated with corticosteroids only (i.e. immunosuppressive monotherapy) maintained a proteinuria level lower than 1 g/day for the entire 36-month follow-up period (Supplementary data, Appendix, Table S2). This indicates good efficacy of corticosteroids, at least in this group of patients receiving immunosuppressive monotherapy. We cannot exclude that in a longer follow-up the benefits on renal function would appear. Why was the use of corticosteroids in combination with other immunosuppressants ineffective in patients with reduced renal function? This is strange, because this result seems at odds with findings from the VALIGA study [10] and another randomized controlled trial in patients with a mean estimated glomerular filtration rate of 29 mL/min/1.73 m² [11]. Unfortunately, the STOP-IgAN study lacked certain elements for a more useful evaluation. In particular, the authors did not consider the role of histological lesions in the progression of renal disease and in the response to treatment. Thus, the lack of this histological evaluation does not allow us to understand if response to treatment can also be determined by the type and degree of histological lesions, as suggested by the Oxford classification of IgAN [12]. Fortunately, since Rauen has all the histological data obtained from the renal biopsies, this evaluation can still be made.

SUPPLEMENTARY DATA

Supplementary data are available online at http://ndt.oxfordjournals.org.

CONFLICT OF INTEREST STATEMENT

None declared.

REFERENCES

A Polar Views discussion by Pozzi and Rauen et al. on the interpretation and clinical application of the recently published Supportive Versus Immunosuppressive Therapy of Progressive IgA Nephropathy (STOP-IgAN) trial has elucidated important points concerning potential strengths and weaknesses of this landmark randomized trial. This critical examination of the impact of steroid monotherapy or steroid plus an immunosuppressive (IS) agent compared with ‘supportive’ therapy with inhibitors of the renin–angiotensin system (RAS) has enhanced our appreciation of the importance of rigorous application of titrated RAS inhibition in high-risk patients with persistent proteinuria >0.75 g/day. At the same time, it brings a new level of uncertainty concerning the overall value and risk of steroid or steroid plus IS therapy in patients failing such ‘supportive’ therapy. Some of these uncertainties revolve on issues of study design, such as the duration of follow-up, participant stratification (particularly underlying pathology) and dosing regimens. It is hoped that additional trials, better methods of patient selection, improved surrogate end points and safer regimens will lead to less uncertainty over the best treatment practices. On balance, the STOP-IgAN trial raises some key concerns about the merits of steroid alone or steroid plus IS therapy for selected subjects with IgAN, but it does not by itself close the door on the utility of steroid monotherapy in subjects with high-risk IgAN, even as it further degrades the value of steroid plus IS, at least with sequential cyclophosphamide and azathioprine.

**Keywords:** IgA nephropathy, immunosuppression, steroids

Experienced physicians are accustomed to living with uncertainty, both in regard to diagnosis and treatment. Many examples of this common occurrence are found in the discipline of nephrology, and the treatment of IgA nephropathy (IgAN) is among the more prominent ones in this genre. IgAN is frequently encountered in the practice of nephrology, and a new diagnosis of this disorder raises concerns about future progression in the mind of both the physician and patient. Overall, IgAN progresses to end-stage renal disease (ESRD) requiring renal replacement therapy in ~10–40% of patients over a long period of time, often 15–20 years [1, 2]. The variability is contributed to by policies for biopsy of patients suspected of having IgAN and by the severity of disease at the time of definitive biopsy diagnosis of IgAN [1, 2]. Spontaneous remissions are infrequent, at least in adults [3]. Identification of patients most likely to progress (high risk) can be reasonably well defined at the time of diagnosis by several means.

Impaired glomerular filtration rate (GFR; relative to that expected for the patients’ age), hypertension, obesity, persistent high-grade proteinuria (>1.0 g/day), levels of circulating IgG/IgA antibodies to aberrant glycoforms of IgA1, hyperuricemia and hyperlipidemia are a few of the clinical and laboratory indicators of a poor renal prognosis [4–7]. The severity of