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COMMENTARY

Is it time for personalized therapy in IgA nephropathy patients?

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Roccatello et al. [1] investigated the effectiveness and safety of mycophenolate mofetil (MMF) in combination with corticosteroids, compared to a 6-month course of glucocorticoids alone, in a group of 30 patients with proteinuric immunoglobulin A nephropathy (IgAN) who had active renal lesions (including proliferative endocapillary and extracapillary lesions and fibrinoid necrosis) identified through kidney biopsy. All patients received renin-angiotensin system blockers (RASBs) at the maximum tolerated dose as supportive therapy. The retrospective study demonstrated a significant reduction in proteinuria in both patient groups, with the mean follow-up period being 18.7 months for the first group receiving MMF in combination with corticosteroids, and 21.5 months for the group treated with corticosteroids alone. At the end of the follow-up period, the authors obtained a cumulative sparing dose of 6 g of corticosteroids in the group of patients who received the combined therapy (MMF and corticosteroids).

The study is limited by its retrospective design and the small number of patients included. However, it highlights two important points: first, the central importance of kidney biopsy in determining therapy for IgAN patients, and second, the potential for MMF to reduce the overall dose of corticosteroids required for treatment.

An international group of nephrologists dedicated 6 years (2004–2009) to developing the Oxford classification of the renal lesions in kidney biopsy from IgAN patients. Briefly, the classification is based on the grade of histological lesions as mesangial proliferation (M0,1), endocapillary proliferation (E0,1), glomerular sclerosis (S0,1) and tubulointerstitial lesions (T0,1,2). Eight years later, in 2017, the classification was revised and extracapillary proliferative lesions (C0,1,2) were included [2]. Thus, active renal lesions (E1 and C1,2) were differentiated from chronic renal lesions (T1,2). Unfortunately, the renal lesions were not considered in the first and second release of the KDIGO guidelines [3]. It is recommended that all patients receive intensive supportive therapy (renin-angiotensin system blockers) for at least 3–6 months following kidney biopsy. If the patient remains proteinuric (excreting more than 1 g per day) after this period, corticosteroids may be added to the treatment regimen. This means that active renal lesions become chronic in IgAN patients after 3 months of supportive therapy without immediate immunosuppressive therapy. This non-appropriate procedure has been adopted in all randomized clinical trials (RCTs) in the last 10 years, as shown in Table 1. The time lapse between the kidney biopsy and the randomization procedure fluctuated between 3 and 6 months of supportive therapy. All biopsy-proven IgAN patients (with active or chronic renal lesions) who were enrolled in those studies had chronic renal lesions because active renal lesions were not immediately treated with immunosuppressive therapy. There are several points to consider with this therapeutic approach. Firstly, corticosteroids may not be necessary for treating proteinuric IgAN patients with chronic renal lesions after supportive therapy. Newer drugs such as gliflozins and endothelin angiotensin receptor antagonists, when combined with RASBs, may effectively reduce proteinuria [4, 5]. Secondly, these drugs do not have to be limited to IgAN patients alone, but may also be used to treat other biopsy-proven chronic glomerular diseases. For example, sparsentan was initially shown to be effective and safe in patients with focal and segmental glomerular sclerosis [6] before being tested in IgAN patients [5]. Additionally, it is worth mentioning the targeted-release formulation, budesonide (Nefecon), a corticosteroid that has been shown to reduce proteinuria in IgAN patients. However, it is uncertain whether this drug

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Table 1 Standard time to randomize IgA nephropathy patients in clinical studies

RCT	Authors/Year	Study drug	ST timing	Data on kidney biopsy
STOP- IgAN	Rauen T et al. (2015)	ST + immunosuppression vs ST	6 months	NRD
TESTING	Lv J et al. (2017)	High dose of MPL vs Placebo	At least 3 months	C lesions not reported
NEFIgAN	Fellström BC et al. (2017)	TRF-Budesonide vs Placebo	6 months	NRD
DAPA-CKD	Heerspink HJL et al. (2020) [4]	Dapaglifozine vs Placebo	At least 3 months	NRD
NEFIgArD	Barratt J et al. (2023)	TRF-Budesonide vs Placebo	At least 3 months	NRD
PROTECT	Heerspink HJL et al. (2023) [5]	Sparsentan vs Irbersartan	3 months	NRD

ST standard therapy (RASBs), *MPL* methylprednisolone, *TFR* targeted-release formulation, *NRD* no reported data

can also reduce active renal lesions. It would be valuable to investigate the potential of Nefecon when combined with an antiproteinuric drug in treating IgAN patients with active renal lesions following kidney biopsy. Unfortunately, this hypothesis cannot be proved by the NEFIGAN and NEFIgArD studies because all patients received RASBs alone for at least 3 months before Nefecon therapy.

The use of MMF therapy for IgAN patients has been extensively studied by various investigators. The final conclusion, as reported in KDIGO guidelines [3], is that this drug should only be given to Asian patients since randomized clinical trials in Caucasian IgAN patients have not shown significant benefits. Peng et al. conducted a recent meta-analysis of nine randomized controlled trials involving 587 IgAN patients. Their findings indicate that the combination of MMF and medium/low doses of steroids had comparable efficacy to full doses of corticosteroids, but with reduced side effects from steroids [7]. These findings support the conclusions of Roccatello et al. [1], who observed a reduction in corticosteroid use with fewer side effects. Additionally, in the MAIN trial, Hou et al. [8] demonstrated that adding MMF to supportive therapy significantly reduced the risk of kidney damage progression in IgAN patients compared to supportive therapy alone. In this study, 40% of patients had active renal lesions (E1 and/or C1,2). This means that immunosuppressive therapy in combination with supportive therapy may be beneficial in repairing active renal lesions. However, in this study, as in other RCTs, a stratified analysis based on specific renal histology findings has not been done.

In conclusion, results from retrospective studies should be validated by RCTs, but the time between biopsy and randomization must differ in the presence of active and chronic renal lesions. Patients with active renal lesions should begin treatment within two weeks of kidney biopsy, and if they are treated with MMF, lower doses of corticosteroids could be used. There is a wide variety of non-steroidal drugs available for treating patients with chronic renal lesions. Tailoring treatment based on the results of kidney biopsy is necessary to achieve a personalized therapy for IgAN patients. A new randomized controlled trial, the CLIgAN study [9], was recently designed based on the concept of personalized therapy and is currently under way.

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Data availability No datasets were used.

Declarations

Conflict of interest All authors declare that they have no conflicts of interest.

Ethical approval There are no human participants.

Informed consent Not necessary.

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