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Corticosteroids in Patients With IgA Nephropathy: Is the Lower the Better?

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Since its first description in 1968 by J. Berger *et al.*,[1] IgA nephropathy (IgAN) has been mainly characterized by the eponymous IgA. Since then, key pathogenetic contributors have been unraveled involving distinct predisposing susceptibility gene loci, a disturbed gut-kidney axis, aberrant glycosylation within the hinge region of IgA molecules, formation of immune complexes and glomerular damage, and complement-mediated processes.[2] All this has been incorporated into the "multiple hit theory" which summarizes a pathogenetic cascade leading to progressive loss of kidney function and kidney failure in most cases. As such, IgAN shares multiple features of classic autoimmune diseases, however it lacks a "diagnostic" autoantibody profile that might be detected in patient serum. The value of a systemic immunosuppressive therapy-as used in classic autoimmune diseases-is intensively debated for patients with IgAN. Notably, many of these immunosuppressants such as azathioprine, mycophenolate mofetil, rituximab, and others have not been proven to have substantial benefits in the vast majority of patients with IgAN. This is also reflected in the current Kidney Disease: Improving Global Outcomes guidelines that do not recommend these substances routinely.[3] By contrast, there is no doubt that a comprehensive supportive treatment is essential for all patients with IgAN to prevent or at least to slow down a progressive disease course. Beyond this commonly accepted approach, Kidney Disease: Improving Global Outcomes guidelines suggests "that patients who remain at high risk of progressive CKD despite maximal supportive care may be considered for a 6-month course of corticosteroid therapy" after a careful consideration of potential side effects in individual patients. A number of early randomized clinical trials on corticosteroid monotherapy mainly designed >20 years ago attributed beneficial effects on proteinuria and hard end points such as kidney failure. A meta-analysis from 2012 overlooking >530 patients with IgAN found that systemic corticosteroid therapy significantly reduced the risk for kidney failure with a relative risk of 0.32 (95% confidence interval: 0.15–0.67, $P = 0.002$), however this was only true when prednisone doses >30 mg per day or when high-dose pulse intravenous methylprednisolone (MP) were applied, whereas low-dose, long-term corticosteroid use did not.[4]

The Therapeutic Evaluation of Steroids in IgA Nephropathy Global study (TESTING) was designed to finally clarify the long-term efficacy and safety of oral MP on top of routine renin-angiotensin system inhibitor therapy. It was performed as an investigator-initiated, multicenter, double-blind, placebo-controlled, randomized trial including patients with primary IgAN at high risk for disease progression (i.e., proteinuria >1.0 g/d and estimated glomerular filtration rate [eGFR] 20–120 ml/min per 1.73 m^2). After a 3-month run-in phase with optimization of supportive therapy, eligible patients were randomly assigned in a 1:1 mode to either receive oral (MP, 0.6–0.8 mg/kg/d for 2 months with subsequent tapering over 6–8 months) or matching placebo. Recruitment started in 2012 and the study group initially projected a sample size of 503 trial participants. In 2015, the study was prematurely halted upon an interim analysis of the Data Safety Monitoring Committee owing to an excessive rate of serious adverse events, mainly severe infections, in the MP arm. Recruitment for the subsequent 241 participants was continued in 2017 after a substantial amendment of the trial protocol with a reduced starting dose of MP (0.4 mg/kg/d) and addition of antibiotic prophylaxis for pneumocystis pneumonia. Results from the combined study population, that is participants

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with both, high- and low-dose MP induction, and corresponding placebo have already been reported in 2022.[5] The primary endpoint consisted of a composite of first occurrence of a sustained 40% eGFR decline, kidney failure or death due to kidney disease. During the trial 74 participants in the MP arm and 106 in the placebo arm reached this primary endpoint (hazard ratio: 0.53, 95% confidence interval: 0.39–0.72, $P < 0.001$] and both high- and low-dose MP doses were effective. Prespecified secondary end points including defined eGFR drop rates +/− kidney failure and all-cause mortality were also in favor of the intervention arm. Serious adverse events occurred in 11% among patients under MP treatment and in 3% of the patients in placebo arm. There were 6 deaths in the MP arm, 3 in the placebo.

In this issue of the journal, Kim *et al.*[6] report trial results from the reduced-dose MP group comprising 241 patients (i.e., ∼50% of the entire TESTING cohort) recruited between 2017 and 2019.[6] Just like in the main trial, in this subcohort the combined renal endpoint occurred less frequently among patients under the reduced-dose MP as compared with placebo over a median follow-up of 2.5 years (7/121 vs. 22/120; hazard ratio: 0.24, 95% confidence interval: 0.10–0.58, $P = 0.002$). Secondary end points also favored MP treatment over placebo. Serious adverse events occurred to markedly lower frequency (7 serious adverse events in the reduced-dose MP arm vs. 3 events in the placebo arm) than those in high-dose MP (30 vs. 5 serious adverse events).

TESTING was planned to address 1 of the fundamental questions in the field of treatment of patients with IgAN, namely does a short-term corticosteroid therapy over several months prevent a progressive disease course and adverse renal outcomes? Indeed, TESTING tells us that it does so, however only during the active treatment phase whereas mean differences in proteinuria and renal function between MP and placebo disappeared afterwards. Over the median follow-up of 2.5 years in the reduced-dose study population, eGFR curves follow a comparably declining course in both arms. A similar trend was observed in the long-term observation from the STOP-IgAN trial. This multi-centric, randomized study pursued a similar approach in a German IgAN population at risk for a progressive disease,[7,8] i.e., to assess benefits and risks of additional systemic immunosuppression with prednisolone (and other immunosuppressants in selected patients) on top of intense supportive treatment. Additional immunosuppression induced an early proteinuria remission (to below 0.2 g/g 3 years after randomization), however eGFR decline rates were comparable between the treatment groups during the 3-year trial phase. In the subsequent passive follow-up of the randomized STOP-IgAN participants over a median of 7.4 years, there were no differences in the occurrence of a composite renal endpoint resembling the one used in TESTING. As a major contribution of the current TESTING substudy, it suggests that also reduced MP doses mediate the same endpoint effects but convey far less infectious complications and other serious adverse events.

At first glance, TESTING and STOP-IgAN reach opposite conclusions in the prevention of a key composite renal endpoint (sustained 40% eGFR decline, kidney failure or death). Nevertheless, both trials demonstrate that corticosteroids given once over a defined time frame are not suitable to prevent chronic kidney disease progression in IgAN. It is important to recognize that TESTING participants and also the current subcohort, were predominantly recruited among Southeast Asian patients, only 5% to 7% were of European ancestry. It remains speculative whether the observations relate to a higher efficacy of systemic corticosteroids in Asian patients with IgAN. Both, TESTING and STOP-IgAN, consistently demonstrate that corticosteroids may induce an early, but transient proteinuria reduction accompanied by a significant increase in severe serious adverse events during the period of active therapy. We conclude that we need better options in the armamentarium of IgAN therapies that can safely be applied over a longer time frame or have long lasting effects. It is pleasant to see that SGLT2-inhibitors are increasingly used in many countries adding additional value to the supportive care. Data on the use of endothelin receptor blockers are equally promising. Furthermore, novel therapies such as targeted release budesonide[9] and others have successfully reached the stage of approval through regulatory authorities for the treatment of IgAN.

DISCLOSURE

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