FGF23, and cardiovascular disease, identifying FGF4 as the primary receptor mediating the deleterious effect of FGF23 on the heart. Clinical trials are now needed to determine whether reduction of excessive FGF23 production by various approaches or interference with its action on cardiovascular tissues by specific FGF4 inhibitors will be effective in reducing cardiovascular morbidity and mortality in patients with CKD.

DISCLOSURE
CMW declared no competing interests. TBD has been an advisor or consultant to Amgen, F. Hoffmann-La Roche, FMC, Sanofi-Genzyme, and Vifor and a speaker for Amgen, Kirin, and Sanofi-Genzyme.

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glomerular disease

Immunosuppression in IgA nephropathy: how certain are we?
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The optimal role of immunosuppressive therapy in the treatment of IgA nephropathy is controversial. Results of a recently completed randomized controlled trial provide strong support for comprehensive supportive care rather than immunosuppressive therapy in patients at high risk for progression.


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IgA nephropathy (IgAN) is considered an (auto)immune-mediated disease on the basis of a number of experimental and clinical observations.1 Immunosuppressive agents are therefore commonly used in IgAN patients at risk for progressive loss of glomerular filtration rate (GFR), including those with proteinuria above 1 g/d, impaired GFR, hypertension, or some combination of these. Indeed, several randomized controlled trials (RCTs) have reported stabilization of renal function following high-dose corticosteroids,2–5 mycophenolate mofetil,6 or more aggressive combination therapy including cyclophosphamide, azathioprine, and corticosteroids.7 However, other RCTs have demonstrated no benefit from immunosuppressive monotherapy6 or combination therapy.8 Several prior studies were limited by inconsistent renin–angiotensin system (RAS) blockade,4,5,7 raising the question of whether immunosuppressives indeed outperform RAS blockers. While some RCTs have been performed with immunosuppression given on top of consistent RAS blockade,2,3 washout of RAS blockers prior
to randomization likely resulted in the inclusion of patients at low risk for progression.\textsuperscript{2,3}

Against this background, we initiated the STOP-IgAN RCT in 2006.\textsuperscript{7} STOP-IgAN tested a 2-phase approach that was subsequently recommended in the 2012 Kidney Disease: Improving Global Outcomes (KDIGO) guidelines,\textsuperscript{10} namely to first uptitrate supportive care over 6 months, thus selecting for high-risk IgAN patients, and then to only consider immunosuppression in such patients (defined as exhibiting proteinuria of \( \geq 0.75 \) g/d, hypertension, and GFR above 30 ml/min per 1.73 m\(^2\)). Supportive care optimization aimed for a blood pressure around 125/75 mm Hg, continued uptitration of RAS blockers in the presence of persistent proteinuria >1 g/d, smoking cessation, avoidance of nonsteroid analgesics, and lowering of elevated cholesterol with a statin (Table 1). It is important to keep this comprehensive approach in mind, as it is not possible to distinguish which of the supportive care interventions were more or less important for the trial outcome. Once this optimization of supportive care had been achieved, participants entered the 3-year study phase and were randomized to continue supportive care alone or to receive additional immunosuppression. Immunosuppression was stratified based on GFR level, given the evidence in 2006: patients with an estimated GFR (eGFR) \( \geq 60 \) ml/min per 1.73 m\(^2\) received high-dose corticosteroid monotherapy,\textsuperscript{5} whereas those with an eGFR of 30 to 59 ml/min per 1.73 m\(^2\) were treated with a cyclophosphamide–corticosteroid combination followed by azathioprine and low-dose corticosteroids.\textsuperscript{7}

The key finding of STOP-IgAN was that the primary end point of \( \geq 15 \) ml/min loss of eGFR from baseline occurred at almost identical frequencies in patients receiving supportive care only versus those receiving supportive care plus immunosuppression.\textsuperscript{5} Secondary analyses based on absolute change in eGFR or creatinine clearance were consistent with this observation. Immunosuppression led to a transient decrease in proteinuria below that in supportive-care-only patients and induced more full remissions (proteinuria of \( <0.2 \) g/g and eGFR loss of \( <5 \) ml/min), particularly in patients with low baseline proteinuria. Serious adverse effects—in particular, infections, incident diabetes, and weight gain—were more common in the immunosuppression group, and 1 patient died from sepsis with the combination regimen. We concluded that our comprehensive supportive care approach reduced annual eGFR loss to such a low level (about \(-1.5 \) ml/min/yr) that it abolished any added benefit of immunosuppression. Notably, our annual eGFR loss was much lower than that observed in the placebo arm of previous RCTs of immunosuppressive therapy.\textsuperscript{2,4,7}

It is important to note several limitations. At the end of run-in, patients with proteinuria above 3.5 g/d, an eGFR \(<30 \) ml/min per 1.73 m\(^2\), or an eGFR decrease of \( >30\% \) from the beginning of run-in were not randomized. Such patients constituted less than 10% of our large study population. There is relative consensus in the KDIGO guidelines\textsuperscript{10} not to consider immunosuppression in IgAN patients with eGFR below 30 ml/min. The only exception is the rare patient with a rapidly progressive course and widespread glomerular necrosis and crescents. However, albeit commonly used, the value of immunosuppression in these patients is also not well established, and immunosuppressive therapy failed to prevent a dismal outcome in a large retrospective series.\textsuperscript{11} So what about patients who still exhibit high-grade proteinuria despite optimization of supportive measures? Retrospective data suggest that patients with proteinuria above 3 g/d derive particular benefit from corticosteroids.\textsuperscript{12} Thus, it remains to be tested in a prospective fashion whether such patients are candidates for high-dose corticosteroid therapy.

### Table 1 | Supportive therapy in IgA nephropathy based on the recommendations in the STOP-IgAN trial\textsuperscript{7}

- Blood pressure control (sitting systolic blood pressure <125/75 mm Hg)
- ACE inhibitor or ARB therapy with uptitration of dosage\textsuperscript{a}
- Sodium restriction
- Control dietary protein intake if GFR <60 ml/min
- Consider a statin if total cholesterol exceeds 200 mg/dl
- Control each component of the metabolic syndrome
- Aldosterone antagonist therapy if proteinuria is not controlled with ACE inhibitor or ARB (possibly add a diuretic to avoid hyperkalemia)
- Smoking cessation
- Avoid NSAIDs, or administer no more than once or twice weekly

\textsuperscript{a}In the STOP-IgAN trial, 35% of the patients received an ACE inhibitor plus ARB combination at the end of the run-in phase.
An important observation of STOP-IgAN was that combination immunosuppressive therapy in IgAN patients at very high risk of GFR decline was ineffective and led to serious complications. This is consistent with trial data from Italy, where the addition of azathioprine to corticosteroids did not improve the outcome, and with observations in Henoch–Schönlein purpura, a systemic form of IgAN, where the addition of cyclophosphamide to steroids added no benefit. These findings are in remarkable contrast to observations made in “true” autoimmune diseases such as membranous glomerulonephritis and lupus nephritis, where corticosteroid monotherapy is usually not sufficient to control the disease and where combination immunosuppressive therapy is the treatment of choice. This contrast and emerging data on genetic susceptibility to IgAN suggest the need to investigate new therapeutic approaches in IgAN, including therapies targeting intestinal mucosal immunity.

So what treatment do we suggest now for the “typical” IgAN patient, namely the patient with moderate proteinuria (1–3.5 g/d), mild to moderate GFR reduction (but still above 30 ml/min), and hypertension? The results of STOP-IgAN provide a strong impetus for optimizing comprehensive supportive care. Only in the rare patient with persistent proteinuria of more than 3 g/d would we consider corticosteroid monotherapy, pending the results of prospective clinical trials. In all others, the risks of immunosuppression seem to outweigh the benefits. Sometimes not doing something may be safer than action.

DISCLOSURE
JF has received consultancy honoraria from Pharmalink, Sweden.

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