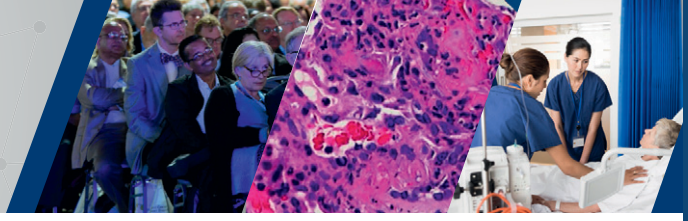

How I Treat IgA Nephropathy

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Introduction

International endeavors to improve the outcome of patients with IgA nephropathy have produced evidence-based treatment recommendations and inspired efforts to develop novel therapies. Clinical trial data highlight the need to individualize treatment and optimize safety. In this article, we describe our approach to the treatment of IgA nephropathy in a commonly encountered scenario—an asymptomatic individual with proteinuria of 1–2 g/d with moderately impaired kidney function. We emphasize the importance of optimizing supportive therapy and making joint decisions around the institution of immunosuppression after consideration of potential adverse effects of corticosteroid therapy.

The Case of Mrs. S

Mrs. S., a 51-year-old White psychologist, was referred for an eGFR of 47 ml/min and proteinuria of 1.7 g/d. Prior medical history included hypercholesterolemia, a resected melanoma in 2005, and recurrent lower abdominal pain. Extensive workup for the latter did not yield a specific cause; in particular, celiac disease and inflammatory bowel disease were excluded. Body mass index was 24.5 kg/m^2, she was a nonsmoker, and BP was below 130/80 mm Hg on 12 mg of candesartan. A kidney biopsy showed IgA nephropathy (MEST score M0, E0, S1, T0, C0). Candesartan was up-titrated to 36 mg/d, and hydrochlorothiazide at 12.5 mg was added. BP fell to levels below 120/80 mm Hg, eGFR 4 months later was 44 ml/min, and proteinuria decreased to 1.36 g/d. She underwent dietary counseling and was advised to engage in endurance activities.

Assessment of Prognosis

A first step in approaching treatment is to consider individual patient prognosis using parameters at the time of biopsy. The International IgA Nephropathy Prediction Tool was derived and validated in large multinational cohorts (1). Although it does not direct specific treatment approaches, the prognostic information is essential to guide joint decisions balancing the risks and benefits of immunosuppression. For this patient, the estimated risk of 50% decline in eGFR or progression to kidney failure at 5 years following biopsy is 12%.

Optimizing Supportive Therapy

As in all glomerular diseases, BP control is the cornerstone of supportive therapy. In IgA nephropathy, BP increases early in the disease, and even though 130/80 mm Hg may be considered "normal," it is higher than that of age-, sex- and body weight–matched controls (2). Consequently, the Kidney Disease Improving Global Outcomes (KDIGO) 2021 guidelines recommend a systolic target in most adult patients with IgA nephropathy of <120 mm Hg measured in a standardized fashion (3) (Figure 1). The second cornerstone is antiproteinuric measures, as reduction in proteinuria is a potent surrogate marker of better kidney outcome (4). In IgA nephropathy, the proteinuria target is below 1 g/d and, ideally, full remission of proteinuria. A strong (grade 1B) recommendation in KDIGO is therefore that renin-angiotensin system blockade should be instituted irrespective of hypertension if proteinuria is >0.5 g/24 h. Dihydropyridine-type calcium channel blockers should not be used as first-line therapy given that they induce preglomerular vasodilation and thereby may increase proteinuria. We also provide extensive lifestyle advice, focusing on dietary counseling for a low-sodium, modest protein–intake diet; normalization of body weight; and engagement in endurance (aerobic) sports while at the same time avoiding high-intensity sports (*e.g.*, lifting of heavy weights); as well as cessation of nicotine consumption.

Immunosuppression

The best available evidence supports the use of corticosteroids in IgA nephropathy, although there must be careful counseling regarding potential toxicity, and we still lack tools to identify individual patients with the best chance of deriving benefit. The early analysis of the TESTING study cohort demonstrated a marked reduction in the composite end point of kidney failure, death due to kidney failure, or 40% loss of eGFR (6% versus 16%; hazard ratio, 0.37; 95% confidence interval, 0.17 to 0.85; P=0.02) in patients treated with corticosteroids compared with placebo (5). A higher risk of serious adverse events, including two deaths, prompted reduction in the corticosteroid dose and addition of *Pneumocystis jirovecii* pneumonia prophylaxis to the study protocol. The recently presented final analysis of 503 patients (with 95% of the patients

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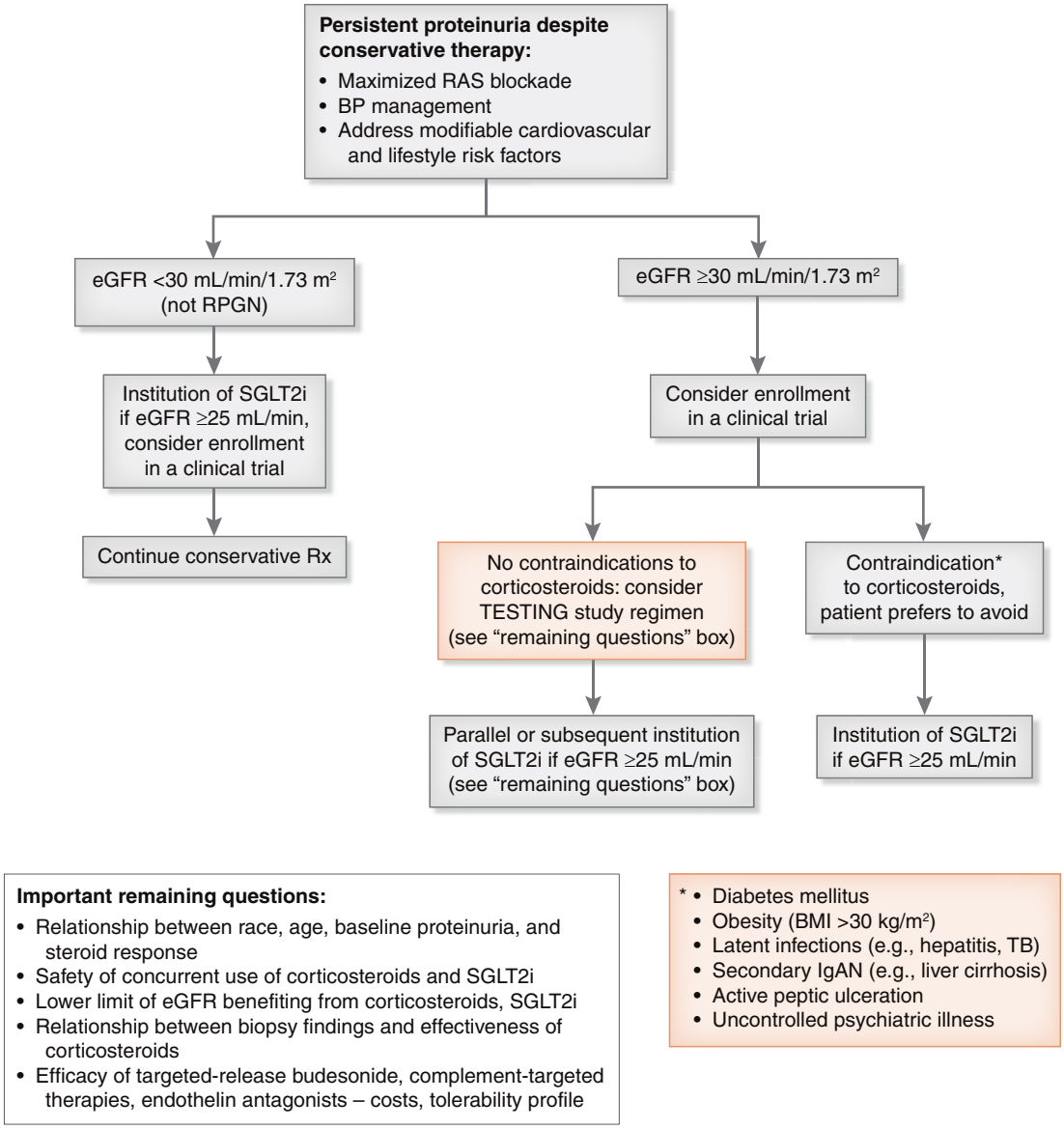

Figure 1. | **Modified Kidney Disease Improving Global Outcomes algorithm, including open research questions.** BMI, body mass index; IgAN, IgA nephropathy; RAS, renin-angiotensin system; RPGN, rapidly progressive glomerulonephritis; Rx, treatment; SGLT2i, sodium-glucose transporter 2 inhibitor; TB, tuberculosis; TESTING, The Therapeutic Effects of STeroids in IgA Nephropathy Global.

from China, Japan, or South Asia; American Society of Nephrology Kidney Week 2021) confirmed the reduction in risk of the composite end point (hazard ratio, 0.53; 95% confidence interval, 0.39 to 0.72; $P<0.001$). This benefit was consistent in patients receiving the reduced dose of 0.4 mg/kg per day of methylprednisolone (maximum: 32 mg/d). Important details regarding the risk of complications will be available with the full publication.

Identifying patients most likely to derive net benefit from corticosteroids remains a challenge. The STOP-IgAN trial in White individuals highlighted the effectiveness of supportive therapies, and despite early reduction in proteinuria immunosuppression, they did not result in long-term prevention of kidney failure (6). It will be critical to understand if the discordant TESTING and STOP-IgAN study findings are a result of differences in the racial, clinical, or histopathologic differences in the two cohorts.

The patient presented here had minimal evidence of proliferation on biopsy, and it is tempting to speculate that residual proteinuria may reflect the segmental glomerulosclerosis. It will be important in the future to determine if there is any relationship between corticosteroid response and specific pathology features, and future clinical trial design and analyses should clarify this relationship. Identifying biomarkers of ongoing inflammation seems even more important to guide decisions regarding immunosuppression.

Alternative Therapies

The potential toxicity and incomplete efficacy of current therapies drive individuals to seek "alternative" treatment approaches. The updated KDIGO guidelines highlight a potential role for tonsillectomy described in patients from Japan; in populations outside of Japan, we do not promote

this procedure: the absence of symptomatic enlarged tonsils with repeated infections associated with synpharyngitic hematuria. Studies of fish oil do not support routine use in IgA nephropathy; although reduction in triglycerides has been described, use of fish oil is also not associated with reduction in cardiovascular events (7).

New Therapeutic Approaches

There is an important unmet need for more effective and safer therapy for progressive IgA nephropathy. The most recent addition to supportive care is dapagliflozin, which markedly reduced progression of IgA nephropathy (8). The safety of combining SGLT2i with high-dose corticosteroids requires further study given the potential risks of ketoacidosis in patients with diabetes or mycotic genitourinary infections. Hydroxychloroquine, 100–400 mg depending on GFR, may also reduce proteinuria, but long-term benefits are unknown (9). Two current phase 3 trials are evaluating combined angiotensin/endothelin receptor blockade *via* sparsentan (the PROTECT trial) or selective endothelin receptor blockade on top of renin-angiotensin system blockade (the ALIGN trial). In a phase 2 trial, targeted release budesonide was shown to stabilize eGFR over 1 year in patients with IgA nephropathy (10); a phase 3 trial (the NEFIGAN trial) is currently ongoing. Whether non-coated budesonide is also effective remains unknown. Other current phase 3 trials in IgA nephropathy focus on complement blockade targeting either activation *via* the mannose-binding lectin pathway (narsoplimab; the ARTEMIS trial; ClinicalTrials.gov identifier: NCT03608033) or the alternative pathway (iptacopan; the APPLAUSE-IgAN trial; ClinicalTrials.gov identifier: NCT04578834).

The Course of IgA Nephropathy in Mrs. S

Her eGFR continued to fall to 38 ml/min, despite a reduction in proteinuria to 1.1 g/d and persistent low BP. One month later, eGFR was 35 ml/min, and proteinuria had increased back to 1.7 g/d. She was advised to stop an herbal medication suggested by a website. A rebiopsy showed some progression in glomerulosclerosis; systemic corticosteroid therapy was discussed but, ultimately, declined. Instead, off-label therapy with budesonide at 9 mg/d was initiated as she had read about early success from the phase 2 study of targeted release budesonide (10). The eGFR continued to drop to 33 ml/min, but proteinuria fell again to 1.1 g/d 3 months following initiation of budesonide. At this point, dapagliflozin had just been licensed for use in any CKD with an eGFR above 25 ml/min in Germany; 10 mg/d was prescribed. At her most recent visit, eGFR was 29 ml/min, and proteinuria had fallen to 0.45 g/d.

Disclosures

J. Floege reports consultancy agreements with Amgen, AstraZeneca, Bayer, Boehringer, Calliditas, Chinook, Novartis, Novo Nordisk, Omeros, Travere, Vifor, and Visterra; honoraria from Amgen, AstraZeneca, Bayer, Boehringer, Calliditas, Chinook, Novartis, Novo Nordisk, Omeros, Travere, Vifor, and Visterra; serving in an advisory or leadership role for Calliditas, Omeros, and Travere; and speakers bureau for Amgen, AstraZeneca, Novartis, and Vifor. H.N. Reich reports consultancy agreements with Calliditas, Chinook, Novartis, Omeros, Pfizer, and Retrophin (Travere); research funding for clinical trial recruitment from Alnylam, Calliditas, Chemocentryx, Omeros, and Pfizer; research funding for serving as a national coordinating investigator from Calliditas and Chinook; honoraria from Novartis; serving on the academic leadership committee for Calliditas, the editorial board of *Kidney International*, and the academic advisory board for Omeros; peer-reviewed funding from the Canadian Institutes for Health Research, the Kidney Foundation of Canada, and the Pearson Foundation; fellowship support from the Fast Foundation; and consultation for the Canadian Agency for Drugs and Technologies in Health.

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Author Contributions

J. Floege and H.N. Reich conceptualized the study, wrote the original draft, and reviewed and edited the manuscript.

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