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IGA NEPHROPATHY – CURRENT AND FUTURE PERSPECTIVES IN TREATMENT

Granak Karol [1,2], Vnucak Matej [1,2*], Beliancinova Monika [1,2], Kleinova Patricia [1,2], Blichova Timea [1,2], Pytliakova Margareta [3], Dedinska Ivana [1,2]

[1]Transplant-nephrology department, University Hospital Martin
[2]Department of I. Internal Medicine, Jessenius Faculty of Medicine, Comenius University
[3]Department of Gastroenterological Internal Medicine, University Hospital Martin, Jessenius Faculty of Medicine of Comenius University

Abstract

Immunoglobulin A nephropathy (IgAN) is the most common primary glomerulopathy in our adult population and is associated with a high lifetime risk of kidney failure. Recent years have succeeded in describing the pathogenesis of IgAN at the molecular level, where immune complexes containing specific galactose deficient IgA1 play an essential role. The gold standard in the diagnosis of IgAN remains renal biopsy followed by determination of a prognostic score using the Oxford classification.

A fundamental goal in the management of patients with IgAN is to optimize supportive therapy involving active lifestyle modification and renoprotective medications. The reno-protective drug menu has recently been expanded to include effective sodium-glucose cotransporter 2 inhibitors (SGLT2i), and additional agents are on the way. However, despite maximal supportive therapy, a wide range of patients remain at high risk of disease progression and require the deployment of immunomodulatory drugs. To date, however, we do not have high potency agents that are well tolerated and safe. This has led to the initiation of many studies to target the inflammatory process at different pathogenetic levels.

In this article, we summarize the current standards in the treatment of IgAN and present new promising options in the management of this disease.

Keywords: immunoglobulin A nephropathy, treatment standards, future perspectives

INTRODUCTION

Immunoglobulin A nephropathy (IgAN) represents the most common primary glomerulopathy in the adult population worldwide and is also the one that most commonly leads to kidney failure (1). Although the disease can occur across all ages, IgAN is rare in the pediatric patient group. Males are more commonly affected and the average age at diagnosis is approximately 40 years (2). The incidence of IgAN is increasing from the West to the East, with the highest incidence in Japan and China (3). IgAN represents the most common finding in renal biopsy in the East Asian (about 40% of histological findings), but also in the Caucasian population (about 20% of histological findings) (2).

IgAN is characterized by the deposition of IgA-dominant or co-dominant mesangial immune complexes. Most of its forms are classified as primary or idiopathic (4). The etiology is unknown, and it is typically considered an autoimmune disease with a multi-hit pathogenesis where 4 major hits play a key role. The first is excessive production of galactose-deficient IgA1 (Gd-IgA1) in the intestinal mucosa. The second hit is the production of IgG autoantibodies directed against Gd-IgA1, which is recognized as an autoantigen. Their reaction results in the formation of circulating immunocomplexes (third hit), which are

Corresponding author: Doc. Matej Vnučák, MD, PhD.; e-mail: vnucak.matej@gmail.com

deposited in the glomerular mesangium (fourth hit) and start a cascade of glomerular inflammation resulting in progressive loss of renal function (5). A smaller percentage of IgAN arise as a secondary form in liver disease (most common), gastrointestinal tract disease (idiopathic intestinal inflammation), autoimmune systemic diseases, or chronic infections. However, there is no consistent definition of the secondary form, nor specific histological findings to differentiate it from the primary form of IgAN (6).

IgAN has an asymptomatic course with gradual slow progression in most cases. The most common clinical and laboratory manifestation in adult patients is the presence of persistent microscopic hematuria and small proteinuria with a gradual decrease in glomerular filtration rate (GFR). Attacks of macroscopic hematuria may be observed in the course of the disease in close succession to infections or physical stress, and this may be the first manifestation of the disease. More aggressive and rapid progression, such as severe nephrotic syndrome or rapidly progressive glomerulonephritis, is rarely encountered (2). In the past, IgAN was considered an indolent disease, but in a large British cohort, the mean renal survival time from the time of diagnosis was 11.4 years, and in a Japanese cohort, 50% of patients progressed to end-stage kidney failure within 30 years (7, 8). The diagnosis of IgAN is purely histological and therefore renal biopsy is essential for confirmation. The latest Kidney Disease – Improving Global Outcome (KDIGO) guidelines for the management of IgAN recommend the use of the International IgAN Prediction Tool, which includes the determination of the histological MEST-C score, to determine the patient's prognosis at the time of diagnosis (9, 10).

Current treatment options

The primary goal of treating patients with primary IgAN is to optimize supportive therapy, which includes active lifestyle modification and the use of renin angiotensin aldosterone system inhibitors (RAASIs) (11). Patients should reduce salt intake to less than 5 grams per day, perform regular moderate physical activity for at least 150 minutes per week, quit smoking, reduce alcohol intake, limit dietary intake of refined sugar, sugar-sweetened beverages, processed meats, and maintain body weight within a body mass index (BMI) range of 20–25 kg/m2 and waist circumference < 94 cm in men and < 80 cm in women (9). The basic and most important measure is to control blood pressure using RAASI with target values up to 120/80 mmHg. All patients with proteinuria > 0.5 gram/day should be treated with RAAS inhibitor regardless of the presence of arterial hypertension (12, 13).

Over the last year, sodium-glucose cotransporter 2 inhibitors (SGLT2i) have become standard in supportive care in proteinuric chronic kidney disease (CKD) (14, 15). Their major impact on slowing the progression of CKD has been demonstrated by The Dapagliflozin in Patients with Chronic Kidney Disease (DAPA-CKD) and Empagliflozin in Patients with Chronic Kidney Disease (EMPA-Kidney) trials (16, 17). In the EMPA-Kidney study, patients with IgAN comprised half of the non-diabetic population (17). Post-hoc analysis of the DAPA-CKD subgroup of 270 IgAN patients showed significant impact on the primary endpoints: a ≥50% decrease in GFR, renal failure or death from renal or cardiac causes [hazard ratio (HR) 0.29, 95% confidence interval (CI) 0.12-0.73], and a concomitant 26% reduction in albuminuria was observed (16). SGLT2i should therefore be part of the basic supportive care in combination with a RAAS inhibitor when the indication criteria are met. Dapagliflozin is indicated in the range of GFR ≥ 25 to ≤ 75 ml/min/1.73m2 and albuminuria ≥ 200 to ≤ 5000 mg/g (examined as albumin/creatinine ratio), empagliflozin can be used from GFR ≥ 20 ml/min/1.73m2.

Further therapeutic intervention should be pursued in those patients who remain at high risk of disease progression (defined by proteinuria ≥ 0.75–1.0 gram/day despite maximum supportive care lasting at least 3 months) (18). Such patients should ideally be enrolled in a clinical trial targeting IgAN. If not available or if the patient is not suitable, immunosuppressive corticosteroid therapy may be considered (9). We have 6–8-month detraction protocols with prednisone according to the STOP-IgAN study or methylprednisolone according to the TESTING study (19, 20). However, it is important to take a strictly individualized approach to this treatment as it may be associated with high rates of toxicity and

unclear clinical outcome. Therefore, the KDIGO guidelines recommend cautious considering their using in patients with GFR < 30 ml/min/1.73m2, diabetes mellitus, obesity, severe osteoporosis, uncontrolled psychiatric illness, latent infection, active gastroduodenal ulcer and possible secondary cause of IgAN (9).

Of the other immunosuppressants, mycophenolate mofetil (MMF) is included in the KDIGO recommendations. However, its use is limited to patients of Chinese origin in whom its effect on maintaining renal function and reducing corticosteroid exposure has been demonstrated. However, studies in the Caucasian population have not yielded a benefit (21). An alternative is the use of the antimalarial hydroxychloroquine in the Chinese population or tonsillectomy in the Japanese population. However, there are no data available to confirm their efficacy in the Caucasian population (22, 23).

New perspectives in the treatment of IgA nephropathy

After the implementation of SGLT2i into the standard supportive treatment of IgAN, the inclusion of other agents can be expected soon. Non-steroidal mineralocorticoid receptor antagonists (MRAs) are now an approved treatment to slow the progression of CKD in patients with diabetes mellitus. Although studies on IgANs are not available, their inclusion in the treatment of non-diabetic CKD, including IgANs, can be expected soon (24). On the other hand, phase 3 trials with endothelin A receptor antagonists (ERAs), namely sparsentan and atrasentan, are currently ongoing. An interim analysis of the PROTECT trial demonstrated a significant reduction in proteinuria and an effect on the decline in GFR after 9 months of treatment in the sparsentan group compared with irbesartan (25). This agent is already registered in several countries for the group at high risk of IgAN progression and we expect its approval in Slovakia as well.

The main disadvantage of corticosteroid therapy is their systemic metabolic and infectious complications. Delivery of corticosteroids to the terminal ileum to act on gut-associated lymphoid tissue (GALT) and minimize their systemic effects is a new breakthrough treatment option to target the site of highest Gd-IgA1 production. Enterosolvent budesonide is the first European Medicines Agency (EMA)-approved agent indicated for patients with IgAN at high risk of progression. An effect in this patient group was demonstrated in the Effect of Nefecon in Patients with Primary IgA Nephropathy at Risk of Developing End-Stage Renal Disease (NefIgArd) study, where the intervention group (enterosolvent budesonide 16 mg daily) achieved a 48% greater reduction in proteinuria after 9 months of treatment compared to placebo. Reported adverse effects, such as hypertension or acne, reflect partial systemic absorption of budesonide (approximately 10% of the dose). However, the absence of an increased risk of infections is essential (26). Registration and use of budesonide in IgAN in Slovakia is currently in process and will be available in practice in the coming months.

Mucosal IgA production is controlled by the cytokines A Proliferation Inducing Ligand (APRIL) and B-cell Activating Factor (BAFF), thus representing another potential therapeutic target. Elevated serum concentrations of APRIL and BAFF have been found in IgAN patients (27, 28). Currently studied agents include monoclonal antibodies against APRIL (siberprenlimab and Bion-1301) and BAFF (belimumab) or decoy receptors for APRIL/BAFF (telitacicept, atacicept). Early data from studies of these agents showed that they effectively reduced circulating Gd-IgA1 levels and significantly reduced proteinuria (29, 30).

Recent years have brought significant advances in the understanding of IgAN pathogenesis, including the role of complement activation. The major activator of the complement cascade in IgAN is the alternative pathway, and C3 deposition in the glomeruli has been shown to correlate with disease progression. The lectin and terminal complement pathways have also been found to correlate with IgAN severity. Glomerular C4d deposition was associated with higher histological disease activity, more rapid decline in GFR and higher risk of renal failure. C5b-9 deposition is associated with renal inflammation and progression of glomerulosclerosis. Conversely, the absence of C1q in most renal biopsies with IgAN suggests that the classical pathway is not involved in the pathogenesis of IgAN (31). Current studies with a wide range of agents inhibiting different stages of the complement cascade are underway

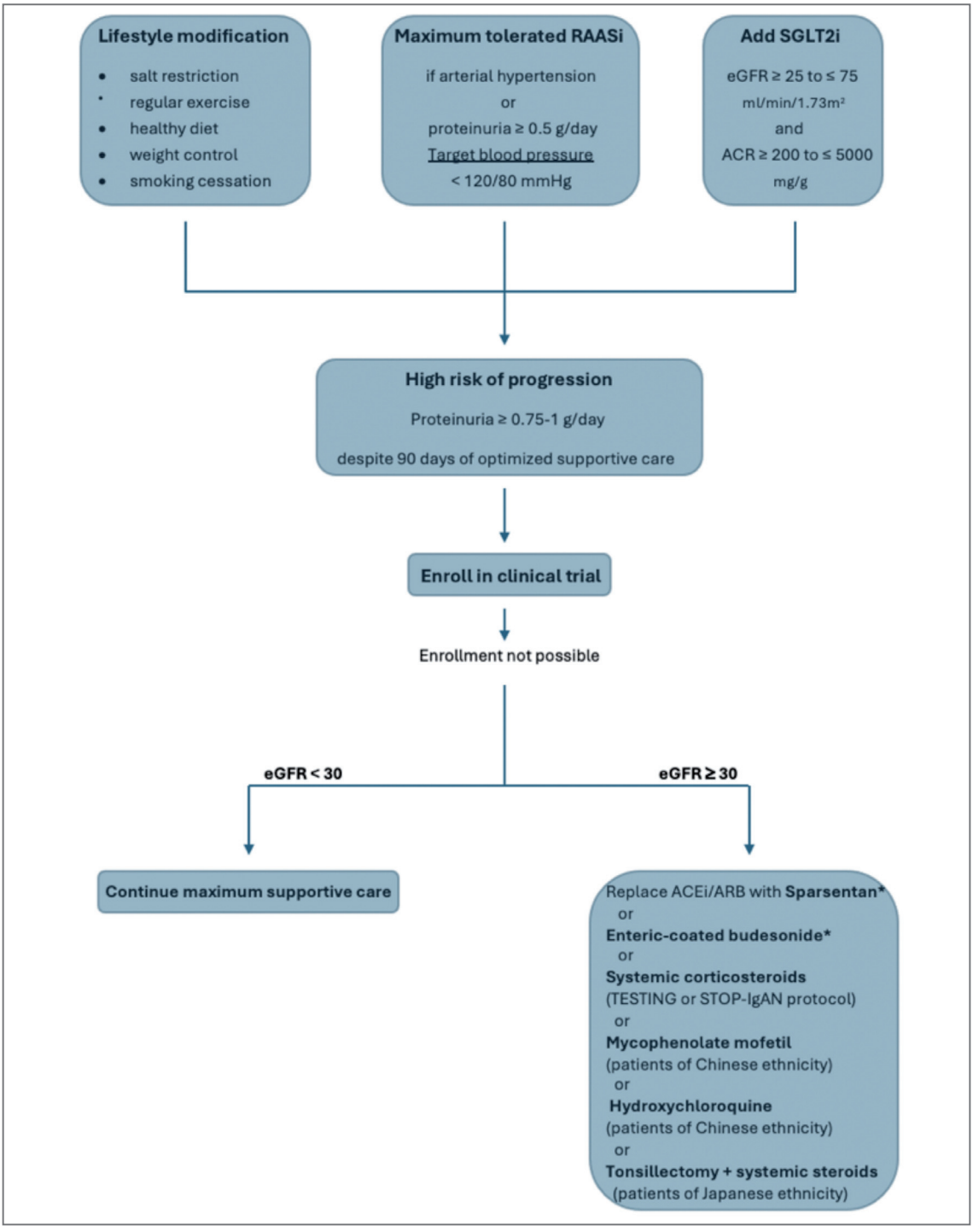

Fig. 1 Recommended algorithm for the management of patients with primary IgA nephropathy. *Sparsentan and enteric-coated budesonide are not yet registered in Slovak republic.
eGFR, estimated glomerular filtration rate; RAASi, renin angiotensin aldosterone system inhibitor; SGLT2i, sodium-glucose cotransporter 2 inhibitor; ACR, albumin creatinine ratio; ACEI, angiotensin-converting enzyme inhibitor; ARB, angiotensin 2 receptor blocker.

suggesting promising results. In the terminal pathway, C3 (pegcetacoplan), C5 (cerndisiran, ravalizumab), or C5a receptor (avacopan) proteins are targeted (32). Other target structures are factor B (iptacopan) and factor D of the alternative pathway or MASP-2 (narsoplimab) of the complement lectin pathway (33, 34).

CONCLUSION

IgAN is associated with a lifetime significant risk of kidney failure, contributing to the disability of the working-age population. Its typical course with slow progression should not lead us to inactivity and a false sense of security. Currently, we have expanded our options to optimize supportive therapy with SGLT2i and, in the near future, ERA and MRA preparations. However, the important fact remains that these treatments do not lead to the prevention of IgA immunocomplex formation and their mesangial deposition. Therefore, immunomodulatory, and anti-inflammatory therapy is also needed in a substantial proportion of patients to suppress these processes (35). To date, we have minimal or no options that are effective, safe, and well tolerated. Suppression of pathogenic IgA production at the GALT (enterosolvent budesonide, inhibition of BAFF and APRIL) in combination with therapies suppressing glomerular inflammation and remodeling (inhibition of complement activation) is likely to make a huge difference in the care of these patients. Treatment will need to be initiated early, simultaneously supportive and disease-modifying.

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