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ЭВОЛЮЦИЯ ВЗГЛЯДОВ НА ПАТОГЕНЕЗ И ЛЕЧЕНИЕ ИММУНОГЛОБУЛИН А-НЕФРОПАТИИ: ЧТО НОВОГО СЕГОДНЯ?

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Evolution of Views on Pathogenesis and Treatment of Immunoglobulin A-Nephropathy: What's New Today?

Резюме

Иммуноглобулин А-нефропатия является наиболее распространенной иммунной гломерулопатией в мире. Значительная эволюция взглядов на патогенез и лечение заболевания особенно заметна в последние годы в связи с появлением новых исследовательских данных. Доказано, что иммуноглобулин А-нефропатия развивается в результате изменения иммунного ответа слизистых оболочек, прежде всего носоглотки (тонзиллит) и желудочно-кишечного тракта. Российскую популяцию пациентов отличает высокая распространенность заболевания, более значительные клинико-морфологические проявления и темпы прогрессирования, более высокая протеинурия и распространенность артериальной гипертензии и более низкая почечная выживаемость, чем в азиатской и европейской популяциях. Иммуноглобулин А-нефропатия является одной из причин развития терминальной почечной недостаточности и необходимости проведения заместительной почечной терапии методами диализа и трансплантации почки, что требует более активного подхода к терапии. Базисом ведения пациентов с иммуноглобулин А-нефропатией, в соответствии с клиническими рекомендациями, является поддерживающая терапия, включающая изменение образа жизни, коррекцию диеты, а также медикаментозную терапию ингибиторами ренин-ангиотензин-альдостероновой системы (иРААС) и ингибиторами натрий-глюкозного котранспортера 2-го типа (SGLT2). Методами лечения, позволяющими уменьшить воспаление в клубочках, являются иммуномодулирующая и противовоспалительная терапия. В представленной лекции изложены основанные на результатах клинических исследований современные взгляды на патогенез, диагностику и лечение (в том числе, на тонзиллэктомию, применение рыбьего жира и различные методы иммуносупрессивной терапии).

Ключевые слова: *диагностика, иммуносупрессивная терапия, ингибиторы ренин-ангиотензин-альдостероновой системы, ингибиторы натрий-глюкозного котранспортера 2-го типа*

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Abstract

Immunoglobulin A nephropathy is the most common immune glomerulopathy in the world. Significant evolution of views on the pathogenesis and treatment of the disease is especially noticeable in recent years due to the emergence of new data on the pathogenesis. It has been proven that immunoglobulin A nephropathy develops as a result of changes in the immune response of the mucous membranes, primarily the nasopharynx (tonsillitis) and gastrointestinal tract. The Russian population of patients is distinguished by its high prevalence, more significant clinical and morphological manifestations and rates of progression, higher proteinuria and prevalence of arterial hypertension and lower renal survival than in Asian and European populations. Immunoglobulin A nephropathy is one of the causes of terminal renal failure and the need for renal replacement therapy using dialysis and kidney transplantation, which requires a more active approach to therapy. The basis for managing patients with immunoglobulin A nephropathy, in accordance with clinical guidelines, is supportive therapy, including lifestyle changes, dietary correction, and drug therapy with renin-angiotensin-aldosterone system (RAAS) inhibitors and sodium-glucose cotransporter type 2 (SGLT2) inhibitors. Treatment methods that reduce glomerular inflammation include immunomodulatory and anti-inflammatory therapy. This lecture presents modern views on pathogenesis, diagnostics, and treatment (including tonsillectomy, fish oil, and various immunosuppressive therapy methods) based on clinical research results.

Key words: *diagnostics, immunosuppressive therapy, renin-angiotensin-aldosterone system inhibitors, sodium-glucose cotransporter type 2 inhibitors*

Conflict of interests

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MCD — minimal change disease, RPNS — rapidly progressive nephritic syndrome, ARB — angiotensin II receptor blocker, IBD — inflammatory bowel disease, HIV — human immunodeficiency virus, CS — corticosteroid, HCQ — hydroxychloroquine, GN — glomerulonephritis, DBP — diastolic blood pressure, ACEi — angiotensin-converting enzyme inhibitors, SGLT-2i — sodium-glucose transporter 2 inhibitors, IGAN — immunoglobulin A nephropathy, IC — immune complexes, IST — immunosuppressive therapy, CG — clinical guidelines, MMP — mofetil mycophenolate, AKI — acute kidney injury, eGFR — estimated glomerular filtration rate, RAAS — renin-angiotensin-aldosterone system, SBP — systolic blood pressure, TE — tonsillectomy, CKD — chronic kidney disease, CP — cyclophosphamide, Gd-IgA1 — galactose-deficient immunoglobulin A1, KDIGO — Kidney Disease: Improving Global Outcomes, FDA — Food and Drug Administration (USA)

Introduction

Immunoglobulin A nephropathy (IGAN) was described first by J. Berger in 1968 [1]. Immunoglobulin A-associated nephropathy is an immune-mediated glomerular disease with a high risk of renal failure. For many years it was stipulated that IGAN described by J. Berger as a mesangial nephritis with hematuria has a benign course. However, currently it has been proven that the disease often progresses to end-stage renal disease. This is demonstrated by the latest data — in particular, the median renal survival in patients with IGAN in the UK is 11.4 years, while the mean age of reaching renal failure/death is 48 years [2]. In Japan 50 % patients with a 30-year history of IGAN have renal failure [3]. The Russian population of patients with IGAN features more severe clinical & morphological manifestations with quicker progression rates than in patients of other ethnicities or geographical locations [4].

The latest clinical guidelines (CGs) on the diagnosis and treatment of IGAN, including the National Russian [5] and KDIGO (Kidney Disease: Improving Global Outcomes) [6] ones, were published in 2021. However, new data about specific pathogenetic IGA mechanisms have emerged within the period after publishing CGs, with prospective treatment methods proposed that are already currently available in the clinical practice.

Today corticosteroids (CSs) are considered the first-line drugs in the disease-modifying immunosuppressive treatment (IST), with their confirmed evidence-based efficacy [7]. However, the use of CSs even in relatively low doses, including in combination with antimicrobial prophylaxis, carries the risk of adverse effects and poor tolerability. New data on the role of the intestinal mucosal immune system and B-cell stimulating cytokines in the disease pathogenesis, as well as on the participation of alternative and lectin complement pathways in the glomerular injury stimulate the analysis of new approaches to IGAN treatment. In particular, a new method of IST with ileal CS delivery has been developed — it provides

efficient treatment with decreased toxicity risks. New nephroprotective drugs (SGLT-2i, sodium-glucose transporter 2 inhibitors) with proven efficacy have been added to practice [8, 9].

Purpose

Informing therapeutic physicians about modern insights into IGAN pathogenesis, diagnostic and treatment methods in accordance with the latest international and national (Russian) clinical guidelines (2021), as well as treatment methods developed recently.

Epidemiology

IGAN is the most common form of primary glomerulonephritis (GN) globally [1, 10]. The prevalence of morphologically confirmed IGAN in Russia among all kidney biopsies was 19.6 % in 2009–2014 and 23.6 % in 2014–2019, while among primary glomerulopathies within the same periods — 32.1 % and 41.2 %, respectively, thus demonstrating an increasing trend from 1999 to 2019 [4]. The results of the study by V. A. Dobronravov et al. (2019) demonstrated a high prevalence of IGAN in Russia comparable to that in Asian countries (28–58 % of all GN types in China, ~47 % in Japan), exceeding that in Europe (10–35 % of all GNs) [11].

Age, gender

The disease is most commonly diagnosed at the age of 20–40 years [1]. It is prevalent in Eastern Asia equally among males and females, while in Europe and North America it occurs 3 times more frequently among males [12]. Based on the retrospective study (2019), in Russia the age of patients with primary IGAN was 34±12 with slight male predominance (55 %) [4].

Pathogenesis

IGAN is an immune complex disease with the formation of immune complexes (ICs), in which galactose-deficient immunoglobulin A1 (Gd-IgA1) is an autoantigen formed as a result of weakened glycosylation of specific regions in this immunoglobulin. Excessive antigenic stimulation of the oropharyngeal tonsillar cells in chronic tonsillitis and cells in the inflamed distal small intestine leads to the enhanced production of weakly glycosylated IgA1 with autoantigenic properties, with the activation of a classic and alternative (including lectin) complement pathways. T-independent IgA production on mucous membranes is regulated by cytokines, including the proliferation-inducing ligand and the B-cell activating factor. Binding with specific receptors, ICs located on mesangiocytes in renal glomeruli lead to the injury of the latter ones with the activation of cytokine and growth factor production by renal cells, with the development of specific morphological alterations. Upper and lower respiratory tract infections, acute bacterial or viral gastroenteritis, other infections, immunizations, ultraviolet radiation can provoke this process [5, 13].

The latest studies have proven the role of the gastrointestinal microbiome and food-borne antigens as triggers of weakly glycosylated IgA1 formation [17]. The association has been detected between the impaired intestinal microbiome and IGAN [14], as well as between the specific microbial counts and the proteinuria level [15]. The role of intestinal microbiome in the pathogenesis of IGAN has been confirmed with the intestinal microbiome modulation using the fecal bacterial transplants in patients, in particular in the Chinese population [16] — in 6 months those patients had their daily proteinuria decreased by 50 %, serum albumin levels increased, and their renal function stabilized. Patients with IGAN also demonstrated the genetic predisposition of the immune system of the intestinal mucosa to pathologies [17].

Inflammatory bowel diseases (IBDs) may cause secondary IGAN and increase the risk of its progression to end-stage renal disease [18]. Enhanced intestinal permeability is one of the factors predisposing to IGAN in IBDs. However, in primary IGAN enhanced intestinal permeability also correlated with elevated serum levels of IgA-immune complexes [19].

IGAN may provoke the production of IgA antibodies against food antigens — bovine serum albumin and β-lactoglobulin of the cow milk, gluten (if eating gluten-containing products, i.e. wheat, rye, barley) [20]. Moreover, anti-tTG2 antibodies were detected in the renal mesangium in a patient with IGAN and celiac disease, while the gluten-free diet led to remission of both celiac disease and IGAN [21].

Based on new data on the pathogenesis of IGAN, new prospectives have been discovered in the approaches to treatment of this disease; new drugs and treatment methods have also emerged and continue to be analyzed, including those aimed at blocking the alternative and lectin complement activation pathways.

Clinical IGAN variants:

- primary IGAN;
- secondary IGAN developing in systemic diseases;
- IGA-vasculitis (Henoch-Schonlein disease).

IGAN may have an asymptomatic course with minimum erythrocyturia or in the form of synpharyngitic macro- or microhematuria, with minimum or even more significant proteinuria, as well as with nephritic or nephrotic syndrome; it may also have a rapidly

progressive course [22]. Any IGAN may clinically manifest with nephritic syndrome (acute, rapidly progressive, chronic) or nephrotic syndrome (provided the associated podocytopathy develops).

Diagnosis

The diagnosis of IGAN may be significantly established only using the morphological examination of the renal biopsy specimen, as no clinical (serum, urinary) biomarkers have been discovered yet [6]. IGAN diagnosis usually includes:

1. Clinical examination that allows to suspect IGAN.
2. Exclusion of secondary IGAN causes.
3. Morphological examination to verify the diagnosis and to clarify the degree of its activity/sclerosis.

1. During the clinical examination, symptoms suspicious of IGAN are detected: darkened urine (hematuria), especially after pharyngitis, respiratory infections; oliguria or polyuria with nocturia (no urinary disorders are possible). History or medical documents may help to detect episodes of hematuria and proteinuria, nephritic or nephrotic syndrome; nasopharyngeal infections (chronic tonsillitis, pharyngitis) and/or inflammatory bowel diseases. *Physical examination* should focus on the detection of edema, hypertension, uremic symptoms, and diseases that may cause secondary IGAN. *Laboratory tests:* urinalysis may reveal dysmorphic red blood cells, albuminuria/proteinuria, decreased or increased osmotic specific urine gravity. IgA levels rise in blood, renal failure signs (azotemia, impaired electrolyte levels, acid-base disorders) are possible. *Instrumental diagnosis* is arranged in accordance with the guidelines on chronic kidney disease (CKD) [22, 23].

2. Searching for diseases that may cause secondary IGAN: liver diseases (cirrhosis, viral hepatitis C, non-alcoholic steatohepatitis), celiac disease, inflammatory bowel diseases (Crohn's disease, ulcerative colitis), viral infections (caused by human immunodeficiency virus (HIV), cytomegalovirus, hepatitis B and C virus), other variable infections (Lyme disease, chlamydial pneumonia, malaria, schistosomiasis), autoimmune and rheumatic diseases (ankylosing spondylitis, rheumatoid arthritis, systemic lupus erythematosus, dermatitis herpetiformis, Sjogren syndrome), psoriasis, respiratory disorders (chronic alveolitis, idiopathic pulmonary fibrosis, cystic fibrosis), malignancies (IgA-myeloma, lymphomas, lung cancer, renal cell carcinoma) [5].

3. Final IGAN diagnosis is established based on the morphological examination of the renal biopsy specimen. Histomorphological examination of the renal biopsy specimen using light microscopy, immunofluorescence, and electron microscopy is a golden standard of IGAN diagnosis, with the minimum scope of light microscopy and immunomorphological examination with the evaluation of glomerular deposits, including IgA, IgM, IgG, complement fractions (C3, C1q) and light Ig chains (kappa, lambda) [23, 24], to use the results in the diagnosis and evaluation of the disease prognosis [6, 24].

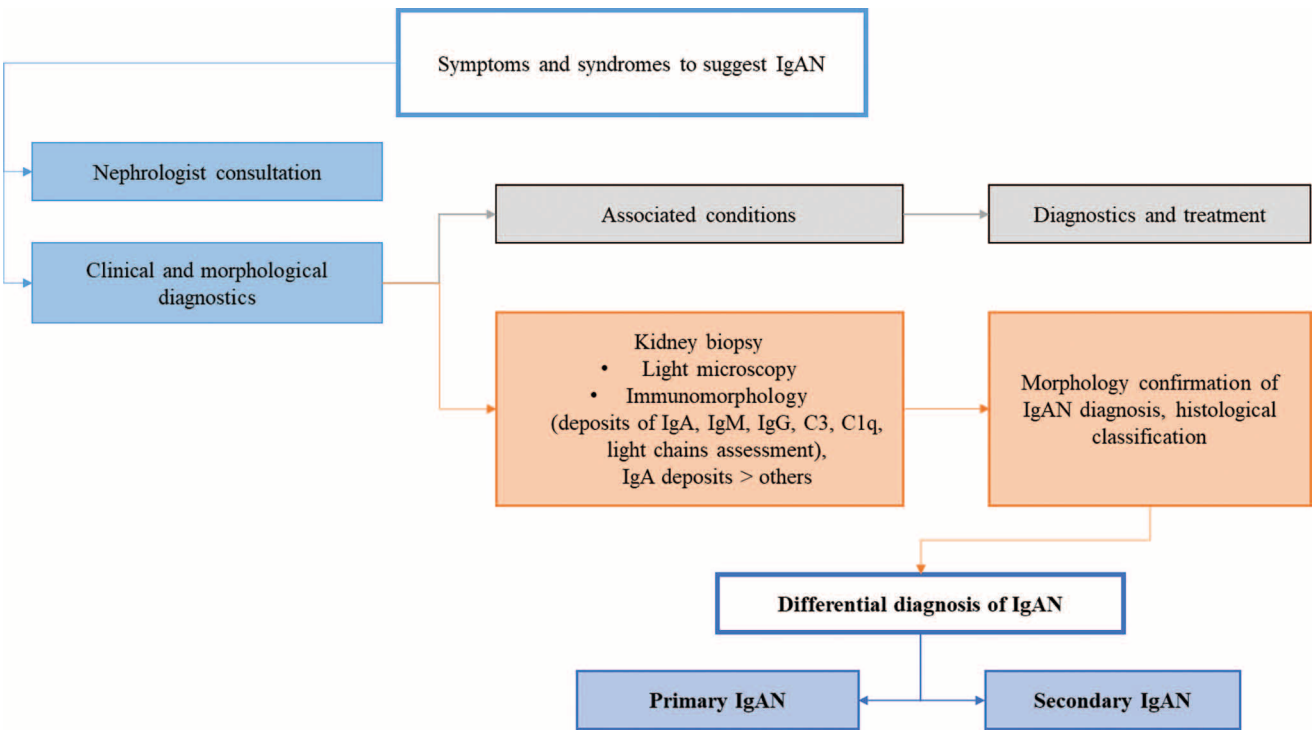

Figure 1. *Diagnostics of IgA-nephropathy [5]*
Notes: IgAN — immunoglobulin A-nephropathy

With that, predominant IgA glomerular deposits is the diagnostic criterion [25] (Fig. 1).

According to KDIGO Guidelines, the renal biopsy specimen is evaluated using the modified Oxford classification (MEST-C scale) using five parameters (M,E,S,T,C): M — mesangial proliferation severity; E — endocapillary proliferation severity; S — presence of segmental glomerulosclerosis or adhesion of capillary loops to the glomerular capsule; T — tubular atrophy/interstitial fibrosis severity; C — presence of cellular or fibrocellular crescents [26]; in Russia this scale has not been validated yet. The scale provides the information on activity and sclerosis, helping to predict the disease outcome [27]. The algorithm of IGAN diagnosis is presented in Figure 1.

Course, prognosis

Renal failure develops in 20–40 % patients with IGAN within 10–20 years after the disease onset [1, 28]. Clinical data, e.g. proteinuria and azotemia, increase the risk of progression. Patients with minimum proteinuria have a low risk of progression; with significant proteinuria and/or increased serum creatinine levels, end-stage renal disease develops in 10 years in 15–25 %, in 20 years — in 20–30 % patients [29].

No validated prognostic IGAN biomarkers are currently available for **prognosis evaluation**, except for estimated glomerular filtration rate (eGFR) and proteinuria. Apart from clinical data, histological results of the biopsy can help to evaluate IGAN prognosis more accurately. IGAN relapses in 20–60 % transplants. It is possible to evaluate the risk of IGAN progression in adults using the online calculator [30], checking the following parameters at the moment of the biopsy: patient's age (in years), eGFR (mL/min/1.73 m^2), blood pressure (BP) systolic and diastolic (mm Hg), daily proteinuria (g/day), information about the use of angiotensin-converting enzyme inhibitors/angiotensin II receptor blockers (ACEi/ARBs) and IST before and after biopsy; histological examination results based on the MEST scale; patient's race. The number of months after biopsy (maximum 80) should also be recorded to calculate the risk. However, it is underlined that the evaluation of IGAN prognosis using this scale cannot form the basis for using any treatment regimens [31]. Disease relapses leads to worsening transplant function and transplant losses in 1.3–16 % cases [32].

IGAN treatment is usually divided into maintenance therapy (aimed at slowing down or preventing the renal failure) [33] and anti-inflammatory or **disease-modifying** therapy (aimed at decreasing the disease activity). The treatment should be started as soon as possible [34].

Maintenance/nephroprotective therapy

This included lifestyle modifications: physical exertion, smoking cessation, body weight control. It is recommended to limit sodium consumption to < 2 g sodium daily (no data on the effects of other dietary recommendations on IGAN outcomes).

Renin-angiotensin-aldosterone system (RAAS) inhibitors. It is necessary to evaluate the risk of cardiovascular diseases and to start the treatment. Systolic blood pressure (SBP) should be maintained at ≤ 120–130 mm Hg, diastolic (DBP) — at ≤ 80 mm Hg. The priority drugs are RAAS, which use slows down the rates of impaired renal function in patients with IGAN vs. no therapy or therapy with another drugs [35].

It is recommended to administer RAAS inhibitors (ACEi or ARBs) in patients with proteinuria over 0.5 g/day even without hypertension in maximum tolerated therapeutic doses in order to decrease proteinuria, which is associated with delayed CKD progression [36]. RAAS inhibitor doses should be maximum (provided the tolerability is good), as nephroprotective effects are achieved with the full-dose treatment [37]. During the maintenance treatment period, patients should regularly undergo examination (every 4–8 weeks), analyzing potassium and serum creatinine levels.

Sodium-glucose cotransporter 2 inhibitors (SGLT2), dapagliflozin or empagliflozin, are administered in addition to RAAS inhibitors in the proteinuric IGAN variant with nephroprotective purposes. Their use significantly decreases risks of fatal and non-fatal events in CKDs of non-diabetic etiology [22]. Dapagliflozin has demonstrated nephroprotective effects, with an average albuminuria decrease by 26 %, delayed CKD progression, decreased mortality from renal or heart failure (based on the DAPA-CKD study) [38]. Dapagliflozin has been recently added to maintenance therapy in IGAN, as it significantly delays IGAN progression [39]. Empagliflozin has also demonstrated similar effects in the EMPA-Kidney study [40], where patients with IGAN constituted 12 % of the total patient population [41]. The results obtained have been confirmed in reviews [42]. At the same time, the safety of concomitant SGLT2 inhibitor and immunosuppressive therapy use is currently unknown.

Fish oil was recommended in previous CGs in IGAN; in the latest national CGs this issue was not discussed due to ambiguous data about its efficacy. Based on data from RCTs, delayed renal function decrease occurred during the treatment of patients with IGAN and proteinuria with fish oil (2.5–3 g/day for 6 years) [43]. However, the positive effect was not confirmed in another randomized clinical trial [44]. Several smaller RCTs and a meta-analysis of studies did not also demonstrate benefits of treating IGAN with fish oil [45].

It is recommended to treat a clinically significant infectious and/or autoimmune inflammation of mucous membranes of any location, achieving the disease remission, in patients with primary IGAN [46]. It is recommended to treat the main pathological process, achieving the disease remission, in patients with secondary IGAN without signs of RPGN, nephrotic syndrome, significant proliferative activity and/or cellular crescents. Some patients demonstrate the resolution of clinical & morphological IGAN manifestations after treating the celiac disease and inflammatory bowel diseases. Antiplatelet agents and anticoagulants are not recommended in the treatment of IGAN due to the lack of evidence of their efficacy.

Tonsillectomy (TE). Frequent exacerbations of IGAN after or in the setting of pharyngitis (synpharyngitic hematuria) may indicate the need for TE. According to national Russian guidelines (2021), TE is recommended in patients with primary IGAN who are scheduled to receive CS treatment (monotherapy or in combination with CP or MMP) before or after CS treatment in the absence of contraindications; however, the evidence of TE efficacy is mainly based on Asian studies and only on a single cohort study among Russian patients with IGAN [4]. Japanese studies have demonstrated the improved renal survival, partial or complete remission after isolated TE or TE in combination with CS pulse therapy [47]; thus, KDIGO (2021) considers TE possible in combination with CSs among the Japanese population patients.

Disease-modifying/immunosuppressive therapy (IST)

It is administered to patients with a high risk of IGAN progression to achieve the disease remission and to decrease the progression rate. Currently, according to the evidence-based medicine, the efficacy of only corticosteroids (CSs) has been confirmed in IGAN, which is reflected both in foreign and Russian national CGs [5, 6, 48].

As IST in IGAN is often accompanied by a high risk of infections or adverse effects, before starting the treatment, it is recommended to evaluate the risk of such complications, providing their prevention in accordance with CGs.

Methylprednisolone efficacy and toxicity were analyzed in patients with IGAN in a TESTING-1 randomized clinical trial; however, it was discontinued prematurely due to a high risk of infectious complications. In the next TESTING-2 trial the decreased methylprednisolone dose (0.4 mg/kg/day) was administered over 2 months, with subsequent tapering over 6–9 months [49]; it was used along with antimicrobial prophylaxis (sulfametoxazole or trimethoprim). No differences were detected in the efficacy, although the number of adverse effects and infections decreased [50].

In the "Intensive Maintenance Therapy + Immunosuppression in IgAN" study, European population patients after 6 months of maintenance therapy [51] were administered only maintenance therapy or in combination with IST. In the IST group, the proteinuria level decreased, while the remission rate increased without differences in the eGFR levels [52].

Corticosteroids have demonstrated efficacy in IGAN [48, 49, 53]. The use of CSs is associated with significantly increased odds of remission and significantly decreased odds of end-stage renal disease. 6-month CS therapy is recommended for patients with primary IGAN and proteinuria > 1 g/day after the inefficacy of 3-month renoprotective treatment [54]: 2 months in the dose of 0.4–0.6 mg/kg/day (not more than 40 mg), with monthly dose tapering by 20 % from Month 3 until complete discontinuation. CSs are more efficient in proteinuria over 2 g/day [4].

The use of systemic CSs in IGAN leads to the increaed risk of their toxic effects in patients with eGFR < 50 mL/min/1.73 m^2. Based on Russian national CGs (2021), it is recommended to avoid their use in patients with eGFR < 30 mL/min/1.73 m^2, with diabetes mellitus, obesity, latent infections (e.g., viral hepatitis, tuberculosis, HIV), active peptic ulcers, severe osteoporosis, or uncontrollable psychic disorders [5]. In such patients the primary treatment should be aimed at maintenance therapy, but not the use of systemic CSs. When using CSs in the dose equivalent to the prednisolone dose ≥ 0.5 mg/kg/day, one should arrange the prophylaxis of Pneumocystis pneumonia along with gastroprotective therapy and prevention of osteoporosis [55].

Budesonide is a CS that has anti-inflammatory effects while directly targeting the intestinal lymphoid tissue (GALT) with the appropriate delivery to the terminal ileum. Budesonide is manufactured in the form of enteric-coated tablets and is approved by FDA (Food and Drug Administration, USA) to treat patients with IGAN and a high risk of progressive renal function deterioration. The NefIgArd study analyzed the effects of budesonide (Nefecon) in patients with primary IGAN and a risk of end-stage renal disease administered in the form of enteric-coated tablets in a dose of 16 mg for 9 months vs. patients administered placebo. Proteinuria improvement in the budesonide group was 48 % higher with the lesser rate of adverse effects typical for CSs, i.e. higher hypertension levels, edema, acne, without the increased risk of infectious complications [56]. One should also be cautious when administering budesonide to patients with obesity or diabetes mellitus.

Using other IST drugs in IGAN. The majority of randomized clinical trials (RCTs) did not demonstrate benefits of other drugs, including in combination with

CSs, over CS monotherapy [57]. No data confirming the efficacy or lesser toxicity of alternating or decreased dose CS regimens have also been obtained. However, Russian national CGs allow to use combined IST in specific IGAN cases resistant to CS therapy [5].

Hydroxychloroquine (HCQ). Russian national CGs (2021) recommend to consider using HCQ to decrease proteinuria and induce disease remission in patients with persisting proteinuria > 1 g/day within 3 months of renoprotective therapy in the absence of RPNS and other contraindications: 6-month oral treatment in the dose 200 mg twice daily with eGFR > 60 mL/min/1.73 m^2; 100 mg orally three times daily with eGFR 45–59 mL/min/1.73 m^2; 100 mg orally twice daily with eGFR 30–44 mL/min/1.73 m^2; 100 mg/day with eGFR decrease by > 25 % or to < 30 mL/min/1.73 m^2, accounting for probable adverse effects. KDIGO (2021) recommends to use HCQ only in the Chinese patient population due to the confirmed efficacy according to the results of clinical case studies and RCTs. Data on using HCQ in Caucasian patients are still lacking [58].

Mofetil mycophenolate (MMP) **in combination with CS** is recommended to consider for 6 months with the purpose of decreasing proteinuria, inducing remission, and decreasing the risk of progression in patients with primary IGAN and proteinuria > 1 g/day, eGFR > 30 mL/min, along with mesangial proliferation and/or crescents, but without signs of RPNS. Sample dosing regimen: induction therapy — orally, 1.5 g/day (750 mg twice daily); maintenance therapy — 0.75–1.0 g/day (in 2 daily doses). The oral CS dose of 0.4–0.6 mg/kg/day for two months, following by monthly daily dose tapering by 20 % within 4 months. KDIGO (2021) recommends to use MMP only in the Chinese population patients, where it preserves the renal function and can decrease CS exposure; however, this drug did not demonstrate positive results in Caucasian patients [59].

Cyclophosphamide (CP). CS administration in combination with CP may be discussed in patients with primary or secondary IGAN with RPNS and severe proliferative activity and/or cellular crescents based on histomorphological examinations to induce the disease remission and to decrease its progression rate [60].

Other immunosuppressants, including azathioprine, rituximab, calcineurin inhibitors are not recommended for use (KDIGO, 2021), as they did not demonstrate clinical efficacy in IGAN [33].

Based on the systematic review of observational studies (in the absence of RCTs), **rituximab** may be beneficial to induce the disease remission and to decrease the immunosuppressive burden in patients with IGA-vasculitis resistant to CSs or other IST drugs, or in the setting of contraindications to them. Drug dosing regimen: 375 mg/m^2 once weekly (4 infusions) or 1000 mg once in 2 weeks (2 infusions) [61].

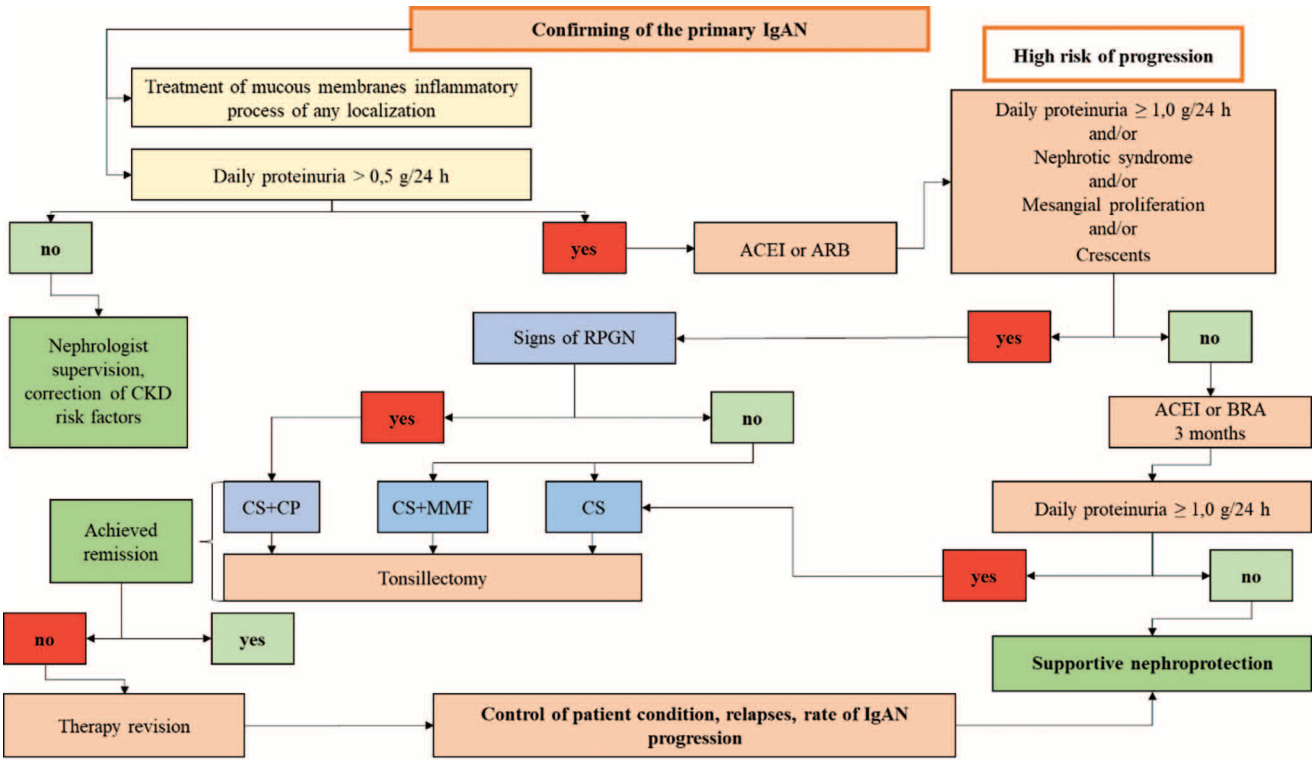

Figure 2. *Management of patients with IgA nephropathy [5]*

Note: ACEI — angiotensin-converting enzyme inhibitors; ARB — angiotensin II receptor blockers; CS — corticosteroids; CP– cyclophosphamide; mycophenolate mofetil — MMF; RPGN –rapidly progressive glomerulonephritis; CKD — chronic kidney disease; IgAN — immunoglobulin A-nephropathy

The algorithm of patient management and treatment based on Russian national CGs (2021) is presented in Figure 2.

Several prospective drugs that can suppress IgA production and control the glomerular inflammation, delaying IGAN progression, are being currently investigated, including endothelin A receptor antagonists (sparsentan, atrasentan), monoclonal antibodies; multiple drugs inhibiting various stages of the complement cascade, including C3 (pegcetacoplan), C5 (cemdirizane, ravulizumab) and C5a receptor (avacopane) that can potentially decrease proteinuria in IgAN. Drugs aimed at alternative pathway factors (iptacopan) and lectin complement pathway blockade (narsoplimab) are also conducted, with their first results confirming their positive effects on proteinuria [62].

Conclusion

IGAN is the most common immune glomerulopathy globally and in Russia; it is one of the causes of end-stage renal disease. The goal of primary care physicians is to improve the clinical diagnosis and refer the patient to renal biopsy, establishing the final morphological diagnosis. One should not be limited by the established practice of only clinical diagnosis and syndrome-wise treatment. The management tactics of all patients with IGAN starts with the maintenance (nephroprotective) treatment, including lifestyle modifications, diet correction, and drug therapy with RAAS inhibitors and SGLT2i (dapagliflozin or empagliflozin). Immunosuppressive therapy (mainly CS with the largest evidence base) is administered with the high risk of IGAN progression. Other IST drugs do not currently have sufficient efficacy, although in cases of high IGAN progression they can be administered in combination with CSs in the setting of lack of efficacy of prior maintenance or CS therapy methods based on the Russian national CGs (2021). The use of budesonide, an enteric-coated CS with target drug delivery to the terminal ileum (with less adverse events typical for CSs), is an innovative method of immunomodulating therapy that has been proposed lately after KDIGO CGs and Russian national CGs (2021) were published. Other treatment methods (tonsillectomy, fish oil) are not routinely administered, but may be discussed depending on the specific clinical situation and patient's race. No safe drugs that can suppress IgA production and control the glomerular inflammation, also delaying IGAN progression, have been basically known until recently, although multiple prospective studies of drugs blocking various mechanisms of IGAN development (i.e. endothelin A receptor antagonists, monoclonal antibodies, inhibitors of various complement cascade stages, alternative and lectin pathway factors) are being currently conducted. The first results confirm their positive effects on proteinuria and, thus, on delayed IGAN progression.

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