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CKJ REVIEW

Expanding options of supportive care in IgA nephropathy

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ABSTRACT

Immunoglobulin A nephropathy (IgAN) is the most common primary glomerulonephritis worldwide, with a potentially serious prognosis. At present, management of IgAN is primarily based on therapeutic lifestyle changes, and excellent blood pressure control and maximized supportive treatment with the combination of inhibition of the renin–angiotensin–aldosterone system with either inhibitors of angiotensin-converting enzyme or angiotensin II receptor blockers and inhibitors of sodium-glucose cotransporter-2, and possibly in the future also with endothelin antagonists. Supportive care currently represents the cornerstone of treatment of IgAN. Targeted-release formulation of budesonide should replace systemic corticosteroids in patients with higher proteinuria and active histological lesions. New treatment options are aimed at immunopathogenesis of IgAN including depletion or modulation of Galactose-deficient-Immunoglobulin A1–producing B cells, plasma cells, and the alternate and/or lectin pathway of complement. The exact place of monoclonal antibodies and complement inhibitors will need to be determined. This article reviews potential supportive therapies currently available for patients with IgAN.

Keywords: angiotensin II receptor blockers, dual inhibitor of ER_A and angiotensin II type 1 receptor, inhibitors of angiotensin-converting enzyme, inhibitors of sodium-glucose cotransporter-2, targeted-released formulation of budesonide

INTRODUCTION

The most common primary glomerulonephritis, immunoglobulin A nephropathy (IgAN), is a dominant cause of end-stage kidney disease (ESKD) and there is an unmet need for novel, more effective and safe long-term treatment targeted at slowing down the progression of this potentially devastating kidney disorder.

Except for lifestyle changes, achieving of optimal body weight, smoking cessation, dietary sodium and in advanced stages also dietary protein restriction, for a long time blood pressure control by inhibition of renin–angiotensin–aldosterone system (RAAS) with either inhibitors of angiotensin-converting enzyme (ACEI) or angiotensin II receptor blockers (ARB) was the only pharmacological option for reducing the rate of loss of estimated glomerular filtration rate (eGFR) before considering systemic corticosteroids in a limited group of patients. Rather disappointingly, even corticosteroids combined with RAAS blockade were shown not to be enough effective in STOP-IgAN and were proven to be toxic in the TESTING trial [1–4]. Therefore, despite emphasizing the importance of best supportive care even in the STOP IgAN trial, substantial numbers of patients suffered from chronic kidney disease (CKD) progression [2] and many patients developed ESKD [2, 5]. Other effective treatment

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Table 1: The list of novel agents tested for IgAN therapy, their modes of actions and NCT number of studies from the ClinicalTrials.gov database.

Agent	Mechanism of action	Studies
Complement-targeted therapy		
Iptacopan (LNP023)	Selective inhibitor of complement factor B	NCT04578834 (recruiting); NCT04557462 (recruiting); NCT03373461 (completed)
RO7434656	Antisense inhibitor of complement factor B	NCT05797610 (recruiting)
Cemdisiran	N-acetylgalactosamine (GalNAc)–conjugated RNAi agent for the treatment of complement-mediated diseases by suppressing liver production of C5 protein	NCT03841448 (active)
Avacopan (CCX168)	C5a receptor inhibitor	NCT02384317 (completed)
ARO-C3	RNAi silencing the hepatic production of complement C3	NCT05083364 (recruiting)
Ravulizumab	Anti-C5	NCT04564339 (recruiting)
Vemircopan (ALXN2050)	Complement factor D inhibitor	NCT05097989 (recruiting)
Pegcetacoplan	Pegylated C3 inhibitor	NCT03453619 (active)
IONIS-FB-LRx (RG6299)	Antisense inhibitor of complement factor B	NCT04014335 (recruiting)
Narsoplimab (OMS721)	Mannan-binding lectin-associated serine protease-2 inhibitor; lectin pathway complement inhibition	NCT03608033 (unknown); NCT02682407 (unknown)
B-cell and plasma cell targeted therapy		
Telitacept (RC18)	Transmembrane binds to and neutralizes the activity of two cell-signalling molecules, BLyS and APRIL	NCT05596708 (not yet recruiting); NCT02808429 (completed); NCT05799287 (not yet recruiting); NCT04905212 (recruiting)
Atacicept	Human recombinant fusion protein that comprises the binding portion of a receptor for both BLyS and APRIL, block of B-cell maturation and survival	NCT04716231 (recruiting)
Rituximab	Anti-CD20, induces B-cell apoptosis and depletion [3]	NCT05824390 (active); NCT02571842 (unknown status); NCT04525729 (recruiting); NCT00498368 (failed—no efficacy)
BION-1301	Anti-APRIL monoclonal antibody with a potentially disease-modifying approach to treating IgAN by depleting Gd-IgA1	NCT03945318 (active); NCT05852938 (not yet recruiting)
Sibeprenlimab (VIS649)	Anti-APRIL	NCT05248646 (recruiting); NCT05248659 (enrolling by invitation); NCT04287985 (active); NCT03719443 (completed—first in human)
Povetacicept (ALPN-303)	Inhibition of BAFF, BLyS and APRIL	NCT05732402 (recruiting)
Other modes of action or drugs without declared modes of action		
Atrasentan	Endothelin A receptor antagonist	NCT04573478 (active, not recruiting); NCT04573920 (recruiting)
Sparsentan	Endothelin A receptor antagonist and ARB	NCT03762850 (active, not recruiting)
Zibotentan + dapagliflozin	Endothelin A receptor antagonist + SGLT2i	NCT04724837 (active, not recruiting)
Felzartamab (MOR202)	Human anti-CD38 antibody (CD38 expressed on activated B and T lymphocytes and on plasma cells)	NCT05065970 (active)
Mezagitamab	Human anti-CD38 antibody (CD38 expressed on activated B and T lymphocytes and on plasma cells)	NCT05174221 (recruiting)
Bortezomib	Proteasome inhibitor	NCT05383547 (recruiting)

RNAi, RNA interference; C, complement; BLyS, B-lymphocyte stimulator.

modalities for patients with IgAN at high risk of progression of kidney function loss are therefore undoubtedly needed. Recently, several novel pharmacological approaches to improve IgAN treatment were introduced (Table 1). In this article we briefly summarize the current state of the art of IgAN treatment and novel therapeutic modalities for this disease, with an emphasis on the supportive care.

INHIBITION OF RENIN–ANGIOTENSIN–ALDOSTERONE SYSTEM

Treatment with ACEI remains a cornerstone of IgAN pharmacotherapy. Administration of ACEI leads to slowing of the progression of renal insufficiency in patients with various renal diseases including IgAN [5, 6]. The renoprotective effect of treatment with ACEI is mediated by decrease of systemic blood pressure and intraglomerular pressure, resulting in decreased protein ultrafiltration, glomerular and tubular protein overload, chronic inflammation, and scarring [1, 5–7] (Fig. 1). It has already been confirmed that proteinuria may be nephrotoxic; reduction of proteinuria is (also in IgAN) associated with ameliorating the progression of CKD. Thus, the Ramipril Efficacy In Nephropathy (REIN) study revealed that ACEI may improve the prognosis of nondiabetic renal disease, with 50% reduction of the risk of progression to ESKD [6, 7]. A further prospective and controlled study demonstrated that ACEI significantly improved renal survival in proteinuric patients with IgAN with normal or moderately reduced renal function [1].

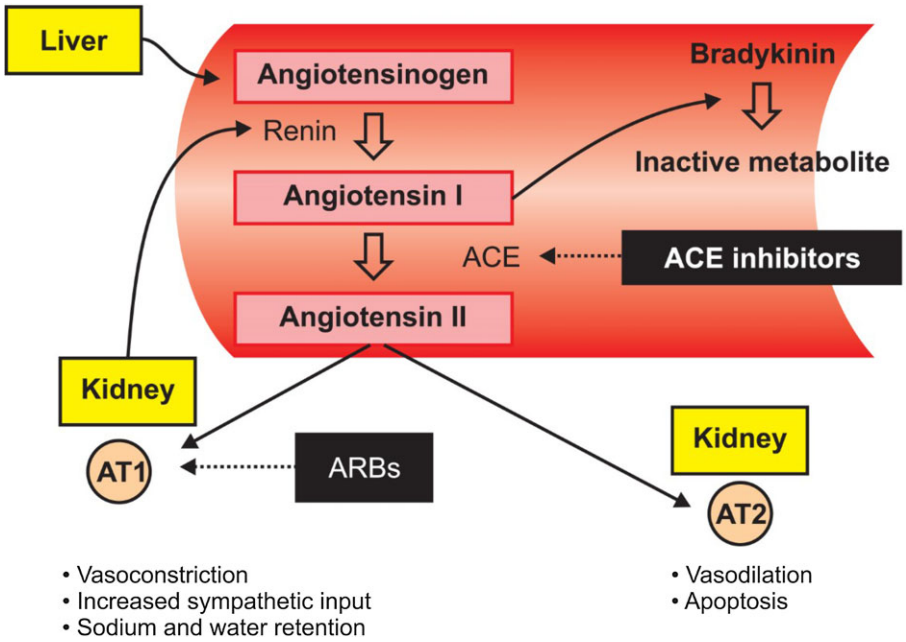

Figure 1: The mechanism of inhibition of renin–angiotensin–aldosterone system.

Other small studies proved that treatment with ARB also decreases proteinuria and prevents deterioration in kidney function in IgAN patients [8, 9], and therefore ARB a treatment alternative for patients who do not tolerate ACEI. Even though combination therapy with ACEI and ARB was tested for possible additional renoprotective effect [10], this combination was abandoned due to the lack of efficacy [11] and increased risk of hyperkalemia shown in the ONTARGET study, where significantly more patients developed potassium levels >5.5 mmol/L in the ACEI + ARB combination arm when compared with monotherapy. Needless to say the ONTARGET study was not focused on patients with IgAN. The extrapolation of the results of ONTARGET study to patients with IgAN is questionable due to low levels of proteinuria in patients in the ONTARGET study [12]. Even though dual combination of ACEI and ARB is often used in real-world practice in patients with IgAN and normal renal function, *post hoc* analysis of the STOP-IgAN trial did not show a positive benefit of dual combination of ACEI and ARB [11].

Most ACEIs are renally excreted and thus accumulated in patients with kidney dysfunction. The only exceptions are fosinopril and trandolapril which are eliminated by both the kidneys and the liver and therefore may represent the preferred agents for patients with CKD. Nevertheless, due to a very good safety profile even renally eliminated ACEI are safe in patients with more severe CKD stages. As the plasma levels of these agents in CKD patients are increased in comparison with patients with preserved normal renal functions, the treatment should be started with low doses and titration up to maximal doses should not be necessary. ARB are almost entirely eliminated via biliary pathway so there is no need for dose adjustment in patients with CKD [13].

As mineralocorticoid receptors (MR) are expressed on podocytes, endothelial and mesangial cells, their blocking prevents glomerular and tubular sclerosis and hence prevents kidney disease progression [14]. Therefore, apart from long-term ACEI and ARB, MR antagonists (MRA) represent an alternative and possibly synergistic approach of RAAS blockade in CKD. When spironolactone or eplerenone were added to ACEI or ARB treatment, they significantly reduced 24-h protein excretion but doubled the risk of hyperkalemia development and have an imprecise effect on GFR [15]. Regarding the mechanism of action of spironolactone, which was the first drug in the class of MRA, it is a partial agonist on MR that also blocks androgen receptors, which leads to adverse drug reactions due to androgen deprivation [14]. Finerenone is a nonsteroidal, selective MRA, which reduced albuminuria, the risks of CKD progression and cardiovascular events (myocardial infarction and heart failure) in patients with CKD and type 2 diabetes [16]. As finerenone has >500-fold less affinity with androgenic, glucocorticoid and progesterone receptors than with MR it has a better safety profile than spironolactone. Nevertheless, all MRAs may induce hyperkalemia which is often dose limiting or even warrants treatment discontinuation [14]. Interesting and promising approach is being carried out on combining MRAs with potassium binders. Agarwal et al. proved that patiromer reduced the incidence of spironolactone-induced hyperkalemia and enables more CKD patients to be treated with MRA [17].

RENOPROTECTIVE EFFECT OF SGLT2I IN IGAN

Treatment with sodium-glucose cotransporter 2 inhibitors (SGLT2i) was suggested as safe and effective treatment when added to standard treatment in patients with IgAN. Several possible mechanisms are proposed as explanation for the renoprotective effect of SGLT2i. The influence on renal haemodynamics is ensured by inhibition of sodium and glucose reabsorption in the proximal tubule with subsequent higher distal delivery of sodium, chloride and water to the area of macula densa, which leads to restoration of possible reduced tubuloglomerular feedback with glomerular afferent arteriolar vasoconstriction and decrease of intraglomerular perfusion pressure and reduction in glomerular filtration [18]. The osmotic effects of higher

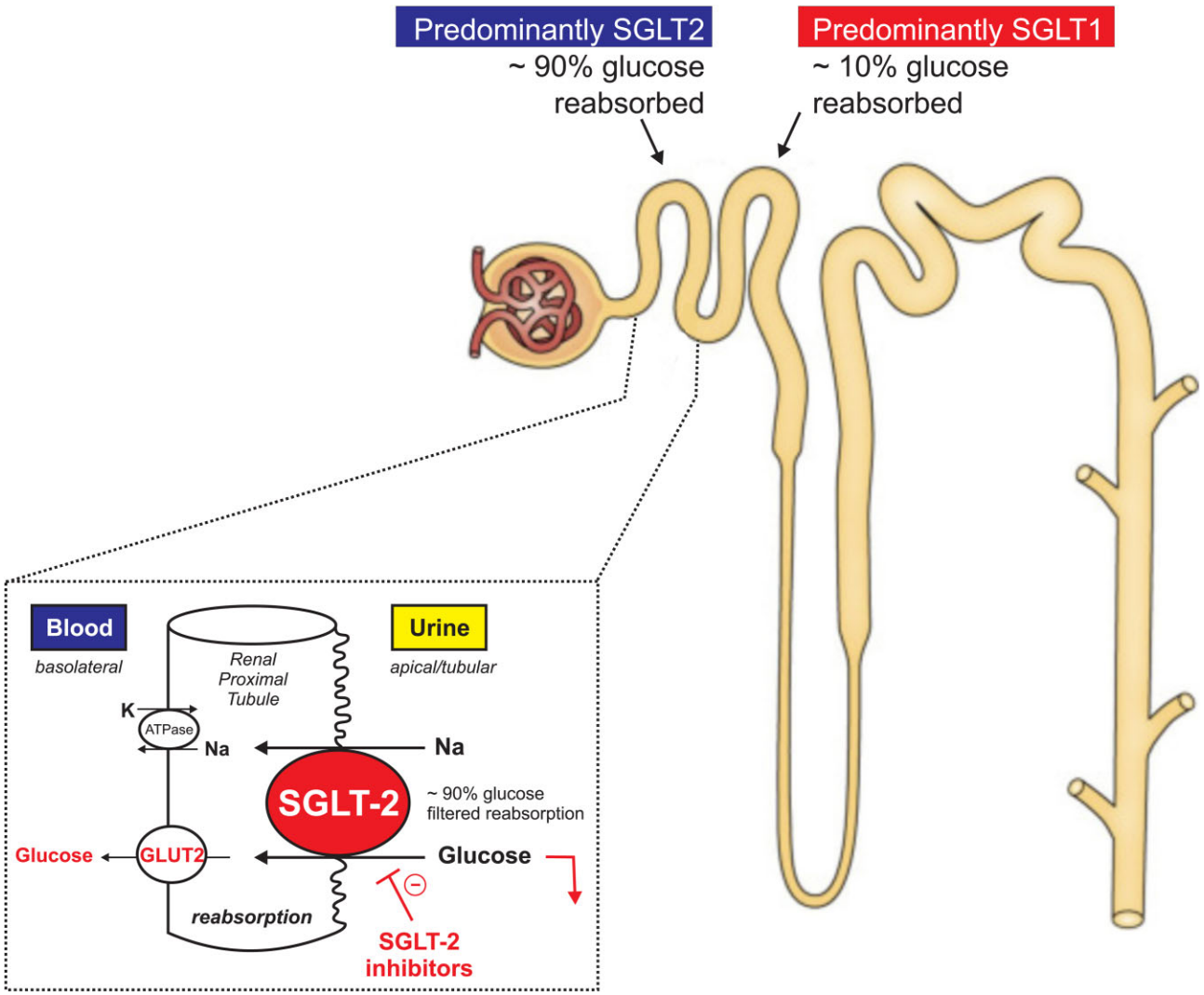

Figure 2: The effect of SGLT2i.

sodium and glucose concentration proceed to the distal nephron with initiation of osmotic diuresis despite upregulation of distal sodium reabsorption [18, 19] (Fig. 2). Subsequently, decreased GFR leads to lower proteinuria with lower direct tubular toxicity. Other proposed mechanisms are reduction of demand for solute transport in the proximal tubular cells and their improved oxygenation, decrease of local pro-inflammatory pathways activity in kidneys and overall metabolic improvement in diabetic patients [18].

An analysis of the DAPA-CKD trial evaluated the effects of dapagliflozin (an SGLT2i) on the kidney and cardiovascular system in 4304 patients with CKD [eGFR 25–75 mL/min/1.73 m^2, albumin/creatinine ratio 200–5000 mg/g (22.6–565 mg/mol)] with or without diabetes. Patients were randomized to 10 mg of dapagliflozin or placebo, as adjunct to standard care. The primary endpoints were decline in eGFR of 50% or more, ESKD, or death from a kidney disease-related or cardiovascular cause. Dapagliflozin reduced the risk of ESKD and extended survival in patients with CKD with and without type 2 diabetes including patients with IgAN [20]. In a subgroup of patients with IgAN [270 participants, 254 (94%) confirmed by renal biopsy] 137 patients were randomized to dapagliflozin and 133 to placebo with median follow-up of 2.1 years. The study was stopped prematurely because patients with dapagliflozin achieved significantly fewer primary endpoints. The primary outcome (sustained decline in eGFR by 50%, ESKD, or death from renal or cardiovascular disease) was found in 6 (4%) patients on dapagliflozin and 20 (15%) on placebo (hazard ratio 0.29; 95% confidence interval 0.12–0.73). Mean rates of eGFR decline with dapagliflozin and placebo were –3.5 and –4.7 mL/min/1.73 m^2/year, respectively. The urinary albumin-to-creatinine ratio was reduced by 26% in patients with dapagliflozin compared with placebo [21]. Dapagliflozin reduced the risk of CKD progression and extended the time of survival in patients with or without diabetes including patients with IgAN [20, 21]. These results have a far-reaching impact on traditional approach to the treatment of CKD associated with proteinuria.

Compared with other clinical trials specific for IgAN, not all patients with IgAN in the DAPA-CKD trial had to be treated by optimal supportive treatment 3 months prior to entry to study. Even though all patients were on a stable dose of RAAS inhibitor for at least 4 weeks before initiation of study it is

not obvious whether patients have been treated by the maximal well-tolerated dose [22]. This may have led to overestimation of the dapagliflozin effect, as lifestyle adjustment, dietary sodium reduction and excellent blood pressure control with maximization of RAAS inhibition also decrease intraglomerular pressure and renoprotective effect. For example in the STOP-IgAN trial, one-third of patients had improved proteinuria level to below the inclusion threshold of 0.75 g/day after optimization of the conservative treatment during the run-in phase and were therefore not randomized into the trial [2]. It is therefore not clear how much additive renoprotective effect might be acquired with SGLT2i in patients with optimized supportive treatment [22].

Needless to say, a crucial key of optimized supportive care in IgAN represents a strict blood pressure control [1, 4]. The association of a renoprotective effect with perfect blood pressure control and decrease of proteinuria has been proven for a long time. In the DAPA-CKD trial, treatment with dapagliflozin was related to substantial decline of blood pressure of around 3–4 mmHg during follow-up [20–22]. This decrease of blood pressure might also be associated with SGLT2i-induced weight loss which represents other important component in conservative treatment in patients with IgAN [22].

So what do we know about the role of SGLTi in treatment of glomerular diseases so far? Maximal tolerated doses of ACEI or ARB for at least 4 weeks were required as one of the inclusion criteria in both studies that proved the effectiveness of SGLTi in CKD patients, DAPA-CKD [21] and CREDENCE [23]. SGLTi are therefore not recommended to institute a renoprotective effect without ACEI/ARB treatment [24]. Should we control eGFR directly after initiation of SGLT2i treatment? Similar to ACEI, early decrease of eGFR of 20%–30% might be expected [21, 23, 24]. Initial decline of eGFR is associated with superior outcome in patients with SGLT2i treatment and might be used for individual assessment of prognosis [18, 24]. Higher serum levels of potassium have not been reported in trials with SGLT2i [21, 23, 24]. Due to the mild diuretic effect of SGLTi, intravascular volume reduction might be associated with the initiation of the treatment. Nevertheless, according to data from Dapagliflozin and Prevention of Adverse Outcomes in Heart Failure (DAPA-HF), diuretic doses may not be modified during SGLT2i treatment as long-term use of SGLT2i induces decrease of interstitial volume rather than intravascular hypovolemia [25, 26].

SGLT2i treatment is commonly restricted to certain eGFR levels, which differ among countries (25–75 mL/min in the Czech Republic), but in clinical trials treatment with SGLT2i was continued up to ESKD without any serious adverse events [21, 24, 27] even though dapagliflozin plasma levels almost double in severe renal impairment and its main (inactive) metabolite is predominantly renally cleared. Due to its mechanism of action which depends on filtered glucose load in proximal tubule, dapagliflozin's glucose-lowering effect is attenuated with decreased kidney functions [28]. Whether this translates into decreased renoprotective and cardioprotective effect remains largely uncertain. The euglycemic ketoacidosis was not noticed in trials with SGLT2i in patients without diabetes [29], nevertheless it is recommended to discontinue SGLT2i in case of fasting, low-carbohydrate diet or planned major surgery [24, 30]. Higher risk of fungal genital infections was also related to SGLT2i but it should be less pronounced in nondiabetic patients with IgAN due to lower glycosuria and insufficient support of candida growth compared with patients with diabetic kidney disease [21, 22].

A new renoprotective drug has been eagerly awaited in non-diabetic CKD patients. The renoprotective effect of the RAAS blockade is well known in non-diabetic patients with CKD and the DAPA-CKD trial revealed an additive effect of dapagliflozin [4, 20]. High cardiovascular morbidity and mortality is a common finding in patients with CKDs and therefore it is also important to point out that dapagliflozin in the DAPA-CKD trial decreased all-cause mortality and cardiovascular morbidity (hospitalization for heart failure and mortality) [19], which contrasts with many previous studies in patients with diabetic kidney diseases that were early terminated due to increased cases of cardiovascular events associated with hyperkalemia [31].

Recently, randomized data support the use of SGLT2i for modifying the risk of kidney disease progression in patients with type 2 diabetes at high cardiovascular risk and also in patients with CKD or heart failure without type 2 diabetes [32]. The EMPA-KIDNEY trial confirmed that treatment with empagliflozin (SGLT2i) led to a lower risk of progression of kidney disease or death from cardiovascular causes than placebo [33].

ENDOTHELIN ANTAGONISTS IN IGAN

Endothelin 1 (ET1) is a potent vasoconstricting agent produced by endothelial as well as some other types of cells. In kidneys, ET1 is produced by glomerular epithelial, mesangial and medullar collecting duct cells. Importantly, there are two types of ET1 receptors, ER_A and ER_B, with different distribution around the glomerulus and collecting system. In CKD, ET1 levels increase which leads to further progression of CKD via ER_A receptor activation, which triggers renal vasoconstriction and activation of RAAS. ER_A activation in podocytes leads to loss of slit diaphragm protein nephrin and disruptions in cytoskeleton with subsequent podocyte detachment. Therefore, ET_A receptor blockade is logical target for possible CKD treatment. Today, several endothelin receptor inhibitors are studied. Kidney endpoint (alteration in eGFR) was reported in clinical trials with the selective ER_A antagonists atrasentan and avosentan, which were tested for diabetic kidney disease, darusentan, primarily tested for resistant hypertension, and dual ET_A/ET_B receptor inhibitor bosentan currently approved for pulmonary hypertension. Dual ER_A and AT_1 receptor antagonist sparsentan is currently being tested for IgAN and focal segmental glomerulosclerosis [34].

Supportive care of patients with IgAN could be enriched with the replacement of RAAS inhibitors by sparsentan, an investigational dual inhibitor of ER_A and angiotensin II type 1 receptor, which can provide further protection and higher decrease of proteinuria in comparison with standard conservative treatment. Interim results of the ongoing phase 3 PROTECT study (NCT03762850) of sparsentan in IgAN demonstrated 49.8% reduction of proteinuria (>3-fold) from baseline after 36 weeks of treatment compared with the active control arm with irbesartan ($P < .0001$) [35].

Tn the PROTECT study, 404 patients with persistent proteinuria despite treatment with ACEI or ARB were randomized 1:1 to receive daily oral doses of sparsentan or the active control irbesartan [36]. Efficacy endpoints include the rate of change in eGFR over 52- and 104-week periods following the first 6 weeks of randomized treatment. Preliminary eGFR data available at the time of the interim analysis showed a potential treatment effect after 2 years of initiation. To date, sparsentan has been well tolerated, without serious adverse events and consistent with the previously observed safety profile [35]. Results from the confirmatory endpoint analysis should be known in the second half of 2023.

Little is known about the pharmacokinetics of sparsentan which have been described only in small studies examining drug–drug interactions. Sparsentan is a P-glycoprotein substrate eliminated primarily by CYP3A4 metabolism. In a study on healthy volunteers P-glycoprotein inhibitor cyclosporine A (CyA) increased the overall exposition 1.7-fold without remarkable prolongation of half-life. Itraconzole—a CYP3A4 inhibitor—increased the exposition 2.7-fold and prolonged the half-life from 9.9 to 21 h. This shows that CyA influenced primarily absorption and itraconazol elimination of sparsentan. Sparsentan itself did not alter the pharmacokinetics of midazolam and therefore is not altering CYP3A4 activity. Sparsentan modestly induced CYP2B6 and decreased exposition of bupropion [37]. A more detailed study on the pharmacokinetics of sparsentan oral suspension already finished the recruitment (NCT05562362) but no results have been posed so far.

The selective endothelin A receptor antagonist atrasentan reduces albuminuria and the risk of renal insufficiency progression in patients with diabetes and CKD. The Study Of Diabetic Nephropathy With Atrasentan (SONAR) study supported a potential role of selective endothelin receptor antagonists in protecting renal function in patients with type 2 diabetes at high risk of developing ESKD [38]. Atrasentan has a half-life of 21 h and is significantly bound to plasma proteins [39]. It is metabolized predominantly by CYP3A enzymes. In line with this, rifampicin significantly shortened the half-life of atrasentan. Nevertheless, surprisingly, rifampicin increased the peak concentration after atrasentan oral administration and did not reduce the overall exposure measured as the area under the curve. This is probably a result of simultaneous CYP3A4 induction and inhibition of various organic anion transporting peptides (OATP) that are responsible for hepatic atrasentan uptake. The effect of rifampicin on OATP is probably transient and decreases the hepatic clearance of atrasentan only when it is administered in the same time as rifampicin, while it may not be significant when administered several hours apart, when effect of CYP3A induction will prevail [40]. The combination of ER_A antagonist and SGLT2i is being evaluated (Table 1).

In general, regarding pharmacokinetics, most endothelin receptor antagonists have a reliable oral bioavailability, are highly protein bound and have an apparent volume of distribution similar to extracellular water (~20 L) [41, 42]. Agents tested for kidney diseases (avosentan, atrasentan and sparsentan) as well as bosentan are predominantly eliminated by hepatic metabolism. Most of the agents have been proven to be substrates of CYP3A family and may therefore be influenced by significant drug–drug interactions [37, 40–42]. Bosentan is not only a substrate, but also an inducer of CYP3A4 and CYP2C9, and therefore may influence co-administered medication including warfarin and CyA. It also has the shortest half-life of the endothelin receptor antagonists and therefore is the only one that must be administered twice daily [41].

OTHER POTENTIAL TREATMENT

Hydroxychloroquine might play a role in the reduction of proteinuria in Asian patients with IgAN [43, 44].

CONCLUSIONS

Today, treatment management of the most common primary glomerulonephritis, IgAN, is still mainly based on therapeutic lifestyle changes and excellent blood pressure control along with maximizing RAAS inhibition, according to KDIGO recommendations (KDIGO 2021 Clinical Practice Guideline for the Management of Glomerular Diseases). Treatment with corticosteroids is indicated in case of more severe proteinuria and nonfulfilment of inclusion criteria for feasible clinical trials [4]. On the basis of the results of the DAPA-CKD trial, SGLT2i on top of maximal tolerated ACEI/ARB will probably become a new standard of care due to its reliable effectivity and safety profile as well as its affordability [24]. Several novel approaches are still being tested, namely oral budesonide as a potential disease-modifying drug, finerenone and endothelin inhibitors, but their place in the treatment algorithm is still less clear as they have not been tested in combination with SGLT2i.

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DATA AVAILABILITY STATEMENT

The data underlying this article are available in the article itself.

CONFLICT OF INTEREST STATEMENT

No conflict of interests.

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