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Treatment of IgA nephropathy; focus on reducing proteinuria by endothelin A receptor antagonists

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ABSTRACT

IgA nephropathy (IgAN) is the most frequent primary glomerulonephritis throughout world and a leading cause of chronic renal failure across with end-stage kidney failure. Proteinuria, as a hallmark of IgAN, is a key driver of disease progression and a strong predictor of poor renal outcome. Despite current standard therapies, including RAAS (renin-angiotensin-aldosterone system) blockade with ACEIs (angiotensin-converting enzyme inhibitors) or ARBs (angiotensin II receptor blockers), many patients continue to experience persistent proteinuria and progressive kidney function decline. This condition emphasizes the need for more effective and targeted treatment strategies. The endothelin pathway, particularly endothelin-1 signaling promotes vasoconstriction, inflammation, and fibrosis, contributing to podocyte dysfunction and renal damage. Endothelin A receptor antagonists demonstrate renoprotective properties through various mechanisms in IgAN. By selectively blocking endothelin A receptors, these agents can improve glomerular hemodynamics by reducing intraglomerular pressure, thereby alleviating the damage caused by excessive pressure and promoting an improved renal environment. This blockade leads to decreased proteinuria, as a crucial factor in the progression of the disease. Furthermore, endothelin A receptor antagonists can also mitigate inflammatory pathways that are activated in response to endothelin-1, reducing renal inflammation and subsequent fibrosis. The efficacy of endothelin A receptor antagonists in the treatment of IgAN has been substantiated by numerous clinical trials. In particular, atrasentan, a specific endothelin-A receptor antagonist, has shown significant promise in reducing proteinuria compared to placebo.

Review

Implication for health policy/practice/research/medical education:
urrent treatment strategies of IgA nephropathy (IgAN) are primarily aim to reduce proteinuria and slow disease progression. Endothelin A receptor antagonists, are promising class of medications which demonstrate capability in addressing the underlying pathophysiology of IgAN.

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Introduction

IgA nephropathy (IgAN), recognized as the most prevalent primary glomerulonephritis globally, with significant risk of chronic kidney disease (1). The pathogenesis of this disorder contains the complex interactions among genetic, environmental, and immunological factors (2), leading to the deposition of IgA1-containing immune complexes in the glomeruli (3) which directing to inflammation, mesangial proliferation, and progressive kidney damage (4). The progress of the disease can be variable, with some patients experiencing stable kidney function while others may experience a progressive chronic renal failure toward end-stage renal disease (5). Several factors can exacerbate IgAN or contribute to disease progression consisting proteinuria (6) which arises from damage to the glomerular filtration barrier (7); since persistent or heavy proteinuria regarded as a strong predictor of disease progression and ongoing glomerular injury and inflammation(8). A recent study by Cattran et al showed that sustained proteinuria or the duration of proteinuria remission has independent prognostic value of IgAN progression (9). Additionally, the study by Tang et al demonstrated a graded association

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between time-varying proteinuria and renal outcome, with higher risk associated with levels ≥0.5 g/d. The risk of kidney failure is especially elevated in patients who had proteinuria levels ≥1.0 g/d before treatment (10). Current standard therapies consisting of RAAS (renin-angiotensin-aldosterone system) blockade consisting ACEi (angiotensin-converting enzyme inhibitor) or ARBs (angiotensin II receptor blockers), have been the cornerstone of treatment for reducing proteinuria and slowing disease progression (11). Several studies showed, patients with IgAN treated with these compounds to control blood pressure have a lower rate of annual loss of kidney function and diminishing proteinuria (12). It should remember that, complete remission of proteinuria is a clear goal in clinical care of IgAN (9). While, current therapies have shown inconsistent efficacy in reducing proteinuria and disease progression and according to their limitations, including incomplete responses or significant side effects, pointed out the need for more targeted and effective treatments (12,13). Recent advances in IgAN have led to the development of novel therapeutic agents aimed at reducing proteinuria and preserving kidney function (14). Several modalities have been addressed to reduce proteinuria in this disease, containing administration of GLT2 inhibitors (15). A recent study by Dong et al showed that sodium-glucose cotransporter-2 inhibitors resulted to a significant decrease in proteinuria in IgAN patients, with a roughly 30% reduction after six months of treatment (16). Previous studies showed that endothelin-1 is a potent vasoconstrictor and pro-inflammatory peptide produced primarily by renal cells, plays a central role in the pathogenesis of glomerular injury and proteinuria in this disease (17). Notably, in IgAN, endothelin-1 is upregulated in response to glomerular inflammation and injury, contributing to vasoconstriction, podocyte dysfunction, and fibrosis (18). Endothelin-1 exerts its effects through two receptor subtypes; endothelin A and endothelin B (19). Therefore, endothelin A receptor activation mediates vasoconstriction, inflammation, and fibrosis, while endothelin B receptor activation can have vasodilatory and protective effects (20). The imbalance between endothelin A and endothelin B signaling in IgAN exacerbates glomerular injury and proteinuria (17). The activation of the endothelin A receptor leads to several pathophysiological effects, including glomerular vasoconstriction, inflammation, and fibrosis, all of which contribute to renal impairment (17,21). As a result, selective blocking of endothelin A receptor, by endothelin A receptor antagonists can counteract the above, mentioned harmful effects (22). In this review we intended to highlight the importance of reducing proteinuria in IgAN management and explores for targeting the endothelin pathway with endothelin A receptor antagonists.

Search strategy

For this review, we conducted a search on PubMed, Web of Science, EBSCO, Scopus, Google Scholar, the Directory of Open Access Journals (DOAJ), and Embase. We utilized various keywords, including IgA nephropathy, endothelin A receptor, proteinuria, endothelin A receptor antagonists, and endothelin-1.

Current standard of care in IgAN

The management of IgAN focuses on slowing disease progression, reducing proteinuria, and preserving kidney function (23). The cornerstone of IgAN treatment is blood pressure control, primarily achieved through the use of RAAS inhibitors, including ACEIs and ARBs (24). These agents have dual benefits as they lower blood pressure and also reduce proteinuria by dilating efferent arterioles, thereby decreasing intra-glomerular pressure (25). RAAS blockade has been shown to slow the progression of kidney disease in IgAN, particularly in patients with significant proteinuria >0.5 g/d (13). In addition to pharmacological therapies, lifestyle modifications play a crucial role in managing IgAN (26). Reducing sodium intake helps control blood pressure and enhances the efficacy of RAAS inhibitors (27). Similarly, smoking is a risk factor for renal disease progression, and quitting can improve renal outcomes (28). Also, maintaining a healthy weight and physical activity reduces the risk of hypertension and metabolic complications (29).

Despite the benefits of RAAS blockade, several studies showed that individuals with IgAN continue to exhibit persistent proteinuria, which is a strong predictor of poor renal outcomes (23,30). Even with optimal dosing and adherence, RAAS inhibitors may not fully normalize proteinuria, particularly in patients with heavy proteinuria or advanced disease (31,32). This incomplete response highlights the need for additional therapies that can more effectively reduce proteinuria and slow disease progression. Furthermore, RAAS inhibitors are generally well-tolerated, but they are not without risks. Common side effects include hyperkalemia or acute kidney injury (33). Long-term administration of these agents requires careful monitoring of kidney function and electrolyte levels (25). Additionally, some patients may not tolerate RAAS blockade due to hypotension or other adverse effects, further limiting their utility (34). A significant proportion of patients with IgAN continue to experience persistent proteinuria despite optimal RAAS blockade and blood pressure control (35,36). This persistent proteinuria is associated with a higher risk of progressive kidney function decline and underscores the need for more effective therapies (37). Novel agents that target alternative pathways, such as the endothelin system or complement cascade, are being investigated to address this unmet

need (38). It is noteworthy that current conventional therapies primarily focus on managing the symptoms (12), rather than treating the underlying mechanisms of IgAN (39,40). Hence, there is a growing recognition of the need for targeted therapies that can modify the disease course by addressing these specific pathological processes. For example, endothelin A receptor antagonists and complement inhibitors are emerging as promising options for reducing proteinuria and slowing disease progression in IgAN (17).

Molecular Mechanisms of Proteinuria in IgAN

Proteinuria is not merely a symptom of IgAN but a critical driver of disease progression (41). The presence of excess proteins in the urine reflects underlying glomerular damage and initiates a cascade of molecular events that exacerbate kidney injury (42). In the setting of IgAN, the presence of abnormal IgA glycoforms, notably galactose-deficient IgA1, leads to inflammation and damage to the glomeruli (43). This condition followed by enhanced production of endothelin-1 and angiotensin II, resulting in blood and protein leakage into the urine (44). Increasing proteinuria amplifies endothelin-1 and angiotensin II, worsening the damage and accelerating the progression toward kidney failure (45). Furthermore, proteinuria induces tubular toxicity that promote tubular damage and interstitial fibrosis, across with disturbance in glomerular filtration barrier (7,46,47). Then, the proximal tubules, which are responsible for reabsorbing filtered proteins, become overwhelmed by this protein overload (48). Protein overload in the proximal tubules activates several inflammatory pathways (49). The nuclear factor-kappa B (NF-κB) pathway upregulates the expression of pro-inflammatory cytokines such as interleukin-6 (IL-6), tumor necrosis factor-alpha, and monocyte chemoattractant protein-1 (49). These cytokines have been linked to the inflammatory milieu initiated by protein injections in the kidneys, causing tubulointerstitial inflammation and fibrosis (50). Moreover, these compounds, recruit immune cells, including macrophages and T cells, to the tubulointerstitial compartment, perpetuating inflammation and further damaging renal tissue (51), as they amplify ongoing renal injury through induction of reactive oxygen species and activation of pathways leading to glomerulosclerosis (52,53). The accumulation of misfolded proteins can overwhelm the cellular protein quality control systems (54), leading to endoplasmic reticulum stress, lysosomal dysfunction and the release of reactive oxygen species and activation of the unfolded protein response (55,56). The unfolded protein response lastly leads to either adaptive survival responses or in cases of prolonged stress, apoptotic cell death (57). Consequently, the presence of heavy proteins in the urinary space causes direct tubular cell injury and activates apoptotic pathways in renal tubular epithelial cells (58). In addition, sustained tubular damage promotes a fibrotic response within the renal interstitium (59). Proteinuria exacerbates this process by enhancing the expression and activation of growth factor-beta (TGF-β) as a central mediator of fibrosis in IgAN (60). The interaction between tubular cells exposed to excessive protein and interstitial fibroblasts stimulates the secretion of extracellular matrix (ECM) components, such as collagen, thereby promoting fibrogenesis (61). Likewise, TGF-β, in turn, further stimulates the production of ECM components, including fibronectin and laminin (62), while also inhibiting matrix metalloproteinases, enzymes that degrade ECM (63). Excessive ECM deposition, disrupting the normal architecture of the kidney and leading to glomerulosclerosis and tubulointerstitial fibrosis (64,65). Subsequently, the stiffening of the interstitial environment contributes to a cycle of injury, resulting in a decreased glomerular filtration rate and, ultimately, chronic kidney disease (66). Moreover, proteinuria promotes epithelial-mesenchymal transition (EMT), a process in which tubular epithelial cells lose their epithelial characteristics and acquire a mesenchymal phenotype (67). During EMT, cells lose expression of epithelial markers like E-cadherin and gain expression of mesenchymal markers such as vimentin and alpha-smooth muscle actin (α-SMA) (68). These transformed cells contribute to fibrosis by producing ECM components and migrating into the interstitium, where they further exacerbate tissue scarring (69,70). Pathological changes like foot process effacement and podocyte injury are associated with proteinuria in IgAN patients (71). Continuous protein leakage causes dysregulation of cellular signaling pathways within resident glomerular cells, propagating apoptosis and contributing to mesangial hyper-cellularity and matrix expansion (72-74). This progression manifests in clinical terms as heightened proteinuria and progressive renal impairment (75). Thus, the presence of proteinuria is not only indicative of underlying renal damage but also serves as a potent stimulus for inflammatory pathways (37). Proteins in the urine can induce a variety of inflammatory responses within the kidney (76). For instance, complement system activation occurs in response to the accumulation of protein in the glomeruli (77). The complement activation products can potentiate mesangial cell proliferation and glomerular inflammation, leading to further deterioration of renal function (78,79).

Reducing proteinuria with endothelin A receptor antagonists

Focus on reducing proteinuria and slowing disease progression, with endothelin A receptor antagonists

emerging as a promising class of agents (80). Endothelin-1, is a potent vasoconstrictor and pro-inflammatory peptide produced primarily by renal cells, that is upregulated in IgAN (17). Endothelin-1exerts its effects through two receptor subtypes: endothelin A and endothelin B, which have opposing roles in the kidney (81). Endothelin A Receptors mediate vasoconstriction, inflammation, and fibrosis (82). Activation of endothelin A receptors contributes to glomerular injury and proteinuria (22). Versus, endothelin B receptors generally have vasodilatory and anti-inflammatory effects (81). They also promote sodium and water excretion, which can help mitigate the harmful effects of endothelin-1 (81). In IgAN, the balance between endothelin A and endothelin B signaling is disrupted, with endothelin A receptor activation predominating (83). This imbalance exacerbates renal injury and highlights the therapeutic potential of selectively blocking endothelin A receptors (80,83). Endothelin A receptor antagonists, such as sparsentan and atrasentan, selectively block endothelin A receptors while sparing endothelin B receptors (84). By blocking endothelin A receptors, these agents improve renal blood flow and reduce intra-glomerular pressure, thereby decreasing proteinuria (17,22). Endothelin A receptor antagonists reduce the production of pro-inflammatory cytokines and inhibit immune cell infiltration, mitigating renal inflammation (17,85). These agents suppress the synthesis of ECM components, slowing the progression of glomerulosclerosis and tubulointerstitial fibrosis (86). Several studies have shown that the administration of endothelin A receptor antagonists, such as sparsentan and atrasentan, leads to marked reductions in proteinuria and stabilization of renal function in patients with IgAN (22). In particular, atrasentan has undergone clinical trials demonstrating its efficacy in reducing proteinuria (87). The dual mechanism, whereby atrasentan improves glomerular hemodynamics while reducing inflammatory responses, positions it as an effective therapy for patients with high levels of proteinuria (88). The clinical utility of endothelin A receptor antagonists in the context of IgAN has been bolstered by a series of well-designed clinical trials. The PROTECT trial, involving a cohort of patients suffering from IgAN, illuminated the benefits of sparsentan, a dual endothelin A receptor and angiotensin II receptor blocker, showcasing a 49.8% reduction in proteinuria compared to traditional treatments like irbesartan (23,89). Such compelling evidence has led to the accelerated FDA approval of sparsentan for specific IgAN patient groups, emphasizing its role in changing the therapeutic landscape for this condition (90). Furthermore, other trials, such as the ALIGN and AFFINITY studies, are ongoing and aim to solidify the established benefits of endothelin A receptor antagonists in reducing proteinuria and improving renal outcomes (87). Similarly, the interim analysis of the APPLAUSE-IgAN trial led to the accelerated FDA approval of iptacopan (Fabhalta) in August 2024 as a first-in-class complement inhibitor to reduce proteinuria in adults with primary IgAN at risk of rapid disease progression (91,92). This approval applies to individuals with biopsy-proven IgAN and a urine protein-to-creatinine ratio (UPCR) of 1 g/g or higher. At nine months, iptacopan significantly reduced proteinuria compared to placebo. A continued traditional approval of iptacopan may be dependent upon verification and description of clinical benefit in the study. Data on the glomerular filtration rate, expected upon the trial's completion in 2025, will be crucial in determining whether iptacopan can slow or halt the decline in kidney function in IgAN patients (91,92). Recently, in a phase III, multinational, double-blind, randomized, controlled trial, Heerspink et al evaluated atrasentan in 340 individuals with biopsy-proven IgAN, urinary protein excretion of at least one gram per day, and a glomerular filtration rate of at least 30 mL/min/1.73 m^2. IgAN cases were randomly assigned to receive either atrasentan (0.75 mg/d) or a placebo for 132 weeks. The study's interim analysis revealed that atrasentan led to a meaningful and clinically meaningful reduction in proteinuria compared to the placebo. The atrasentan cohort showed a -38.1% change in urinary protein-to-creatinine ratio versus -3.1% in the placebo cohort. This indicates a between-group difference of -36.1 percentage points (95% confidence interval, −44.6 to −26.4; P<0.001) (93). Atrasentan has been found to lower albuminuria and correlates with reductions in low-density lipoprotein cholesterol and triglycerides in prior trials (94). Meanwhile, the focus on combination therapies utilizing endothelin A receptor antagonists in conjunction with existing treatments such as sodium-glucose cotransporter-2 inhibitors is also garnering attention, with preliminary results suggesting enhanced renoprotective effects when both agents are used together (95).

Side effects and considerations

Despite the promising outcomes associated with endothelin A receptor antagonists, concerns remain regarding their adverse effects. A prevalent side effect associated with endothelin A receptor antagonists is fluid retention, which may lead to edema and potential complications in vulnerable patient populations. Such risks necessitate careful patient selection and monitoring, particularly in individuals with existing cardiovascular conditions or those taking concurrent medications that can exacerbate fluid retention. In terms of monitoring, attention must be given to renal function and broader metabolic parameters as endothelin A receptor antagonists

may impact liver enzyme levels and electrolyte balances in some patients. Guidelines recommend a widespread approach to patient care, integrating the potential for these adverse effects with their therapeutic benefits to achieve optimal management of IgAN.

Conclusion

Proteinuria is a central feature of IgAN and a key driver of disease progression. It is not only a marker of glomerular injury but also an active contributor to renal damage through mechanisms such as tubular toxicity, inflammation, and fibrosis. Reducing proteinuria is fundamental for slowing kidney function decline and improving long-term outcomes in patients with IgAN. The treatment of IgAN with endothelin A receptor antagonists represents a significant advancement in the clinical approach to this condition. With compelling evidence supporting their efficacy in reducing proteinuria and improving renal health, agents like atrasentan and sparsentan hold promise for better management strategies for IgAN patients. Nevertheless, mindful attention to their side effects, particularly fluid retention, is crucial to ensure patient safety and effective therapeutic outcomes.

Authors' contribution

Conceptualization: Hamid Nasri, Elham Ahmadipour.
Data curation: Hamid Nasri.
Investigation: Hamid Nasri.
Resources: Elham Ahmadipour.
Supervision: Hamid Nasri.
Validation: Elham Ahmadipour.
Visualization: Hamid Nasri.
Writing-original draft: Hamid Nasri.
Writing-review and editing: Elham Ahmadipour.

Conflicts of interest

The authors declare that they have no competing interests.

Declaration of generative AI and AI-assisted technologies in the writing process

During the preparation of this work, the authors utilized Perplexity to refine grammar points and language style in writing. Subsequently, the authors thoroughly reviewed and edited the content as necessary, assuming full responsibility for the publication's content.

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Ethical issues

Ethical issues (including plagiarism, data fabrication, double publication) have been completely observed by the authors.

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