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Safety and efficacy of sparsentan versus irbesartan in focal segmental glomerulosclerosis and IgA nephropathy: a systematic review and meta-analysis of randomized controlled trials

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Abstract

Background Sparsentan has shown positive effects on managing different subtypes of glomerulonephritis. The recent results of trials require a pooled analysis to validate these results.

Aim We aim to assess the safety and efficacy of sparsentan versus irbesartan for patients with IgA nephropathy and focal glomerulosclerosis (FSGS).

Methods We conducted a systematic review and meta-analysis of randomized controlled trials retrieved by systematically searching PubMed, Web of Science, Scopus, and Cochrane through March 2024. We used Review Manager v.5.4 to pool dichotomous data using risk ratio (RR) and continuous data using mean difference (MD) with a 95% confidence interval (CI).

Results Three studies with a total of 884 patients were included. Sparsentan was superior to irbesartan in improving urine protein to creatinine ratio (UP/C) (ratio of percentage reduction 0.66, 95% CI [0.58 to 0.74], $P<0.001$); as well as the proportion of patients achieved complete and partial remission of proteinuria (RR = 2.57, 95% CI [1.73 to 3.81], $P<0.001$) and (RR = 1.63, 95% CI [1.4 to 1.91], $P<0.001$) respectively. Regarding the effect on the glomerular filtration rate, the results estimate did not favor either sparsentan or irbesartan (MD = 1.98 ml/min per 1.73mm2, 95% CI [-1.05 to 5.01], $P=0.2$). There were no significant differences in adverse events except for hypotension, which showed higher rates in the sparsentan group (RR = 2.02, 95% CI [1.3 to 3.16], $P=0.002$).

Conclusion Sparsentan is effective and has a good safety profile for treating FSGS and patients with IgA nephropathy. However, more well-designed RCTs against ARBs, ACE inhibitors, and steroids with larger sample sizes are needed to get conclusive evidence.

Keywords Sparsentan, IgA nephropathy, Focal glomerulosclerosis, Dual endothelin, ACE inhibitors, ARBs

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Introduction

Glomerulonephritis is a group of heterogeneous immune-mediated disorders that cause damage to the glomerular part of the kidneys' nephrons [1]. It is one of the most common causes of renal impairment, with a prevalence of 10–15% of end-stage renal disease cases in the United States [2]. Immunoglobulin A nephropathy (IgAN) and focal segmental glomerulosclerosis (FSGS) are prominent different types of glomerular disorders that are associated with high morbidity and mortality among adults and children [3, 4]. IgAN (Berger's disease) is the most prevalent primary glomerulonephritis worldwide, with an overall incidence of 2.5 cases per 100,000 or more [5, 6]. IgAN could affect all different ages, with the peak incidence in the second and third decades of life and higher rates in the Asian population [7, 8]. The precise mechanism of pathogenesis of IgAN is still not fully understood with the enrollment of multi-hit hypotheses. The abnormal increase in the level of circulating poorly O-galactosylated IgA1, known as galactose-deficient IgA1 (gd-IgA1), is the key finding of the pathogenesis of IgA nephropathy. Direct interaction between gd-IgA1 and autoantibodies forms an immune complex that deposits within mesangial cells, resulting in inflammation and glomerular injury [9, 10]. Clinical manifestations of IgAN are broad and range from asymptomatic hematuria to rapidly progressive glomerulonephritis [11].

FSGS is not a specific disease entity but rather a histopathological pattern of glomerular lesions of different diseases that primarily target the podocytes, so it is considered podocytopathy [12]. FSGS can be classified according to etiology into primary, genetic, or due to secondary causes. Primary FSGS has been associated with circulating permeability factors that cause podocyte effacement and subsequent proteinuria [13]. Infections like Human immunodeficiency virus and medications are common causes of secondary FSGS.

The current guidelines for the treatment of IgAN and FSGS recommend initial optimal supportive care, which focuses on proper blood pressure management and reduction of proteinuria achieved by lifestyle modification and medications that block renin-angiotensin-aldosterone system (RAAS) using angiotensin-converting enzyme inhibitors (ACEIs) or angiotensin II receptor blockers (ARBs) [14, 15]. Several are the compounds proposed as possible anti-fibrotic drugs, due to their direct or indirect effect on fibrosis. In particular, Endothelin receptor antagonists (ERA) (Atrasentan, Avosentan, Sparsentan, TAK-044) attempted to halt fibrosis progression although they showed limited success in clinical practice. In fact, they showed to reduce proteinuria or albuminuria but did not show any effect on GFR decline [16]. Sparsentan is an oral novel dual ERA and angiotensin II receptor antagonist that gained the Food and Drug Administration (FDA) approval in February 2023 for IgAN patients [17, 18]. It is a highly selective antagonist for endothelin type A receptor (ETaR) and angiotensin II receptor type 1, which are involved in the pathogenesis of IgA nephropathy and FSGS [19, 20].

Considering the lack of any prior systematic reviews assessing the efficacy of sparsentan, conducting a comprehensive meta-analysis would be beneficial in validating the outcomes of the current randomized controlled trials (RCTs) and establishing conclusive evidence. Hence, we aim to assess the efficacy and safety of sparsentan versus irbesartan for treating IgA nephropathy and FSGS in adults and children.

Methodology

Protocol registration

We have registered and published the methodological plan for the systematic review and meta-analysis on PROSPERO (CRD42024521451). We followed the Cochrane Handbook of Systematic Reviews and Meta-analysis [21] and guidelines provided in the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) statement [22] (Table S1).

Data sources & search strategy

A literature search was performed, and four databases (PubMed, Cochrane, Web of Science, and Scopus) were searched for published articles up to March 2024 using relevant keywords (Sparsentan OR (angiotensin II receptor antagonist)) AND ((Focal Segmental Glomerulosclerosis) OR (IgA nephropathy) OR FSGS) (Table S2).

Eligibility criteria and study selection

Studies were included if they met the following criteria:

- Population (P): adults and children with FSGS or IgA nephropathy;
- Intervention (I): sparsentan of different doses;
- Comparators (C): irbesartan;
- Outcomes (O): at least one of the primary outcomes (urine protein to creatinine ratio (UP/C) and/or percentage of patients achieving complete or partial remission of proteinuria at any time during the study);
- Study design (S): RCTs;
- Language: only English;
- Timing: no restrictions.

The following criteria were used to exclude papers: The following study types are not considered original: (1) book chapters, reviews, comments, letters to the editor, and guidelines; (2) any other study design other than randomized controlled trials; (3) studies with overlapping or

duplicate datasets; (4) non-human and in vitro experiments; and (5) studies not published in English.

Study selection and data extraction

Search results were exported to Endnote software [23], where duplicates were screened and removed before using Rayyan software [23]. Three authors (AAAE, MAA, and AME) independently reviewed the titles and abstracts of all search results to assess their eligibility for the study. Disagreements were resolved through discussion, with (A.R) intervening if needed. The full-text screening was conducted on eligible articles meeting the inclusion criteria. References of final included studies were retrieved to avoid omitting potential additional studies not included in the initial search. The data of final records, including the year of publication, target population, baseline characteristics, study characteristics, and outcomes, were extracted manually from the articles into a Google sheet by (AAAE and MAA) and reviewed by (AME).

Risk of bias and certainty of evidence

The risk of bias of included clinical trials was conducted according to the Cochrane risk of bias of interventional studies reported in the Cochrane Handbook of Interventions [24]. The risk-of-bias tool (ROB 2) was utilized by (A.R and AME) authors and resolved by collegial discussion.

Assessed outcomes

The primary outcomes of this study include the Change in UP/C from baseline and complete or partial remission of proteinuria based on protein excretion in urine. Secondary outcomes were (1) a change in estimated glomerular filtration rate (eGFR) from baseline, (2) The eGFR total and chronic slopes, (3) Composite kidney outcome, (4) a Change in systolic and diastolic blood pressure (SBP and DBP) from baseline (5) Common adverse events (any treatment-emergent adverse events (TEAEs), serious TEAEs, TEAEs leading to study withdrawal or death, headache, nausea, dizziness, edema, diarrhea, hypotension, and hyperkalemia) experienced by patients. All outcomes were assessed at the last endpoint available for each study.

Statistical analysis

Meta-analysis was performed in the presence of at least two included studies with available data for assessed outcomes using RevMan software v.5.4.1 [25]. Dichotomous data was reported using (RR), and continuous data was reported mean differences (MD) with a 95% confidence interval (CI). If means and standard deviations were not provided, we calculated them from standard errors, 95%CI, or other statistical indices using the RevMan calculator. A random effect model was adopted rather than a fixed effect model, yielding a more conservative estimate of the pooled effect. We used the Chi-square and I-square tests to evaluate heterogeneity; the Chi-square test determines whether heterogeneity exists, and the I-square test determines the degree of heterogeneity. According to the Cochrane Handbook (chapter nine) [26], significant heterogeneity was indicated by an I-square greater than 50%. At the same time, an alpha level of less than 0.1 for the Chi-square test indicated considerable heterogeneity. The level of statistical significance was set to be $p<0.05$.

Results

Literature search and study selection

A total of 1080 potentially relevant records were retrieved by systematic database search. Duplicates ($n=286$) were removed by Endnote software [23]. The titles and abstract screening was conducted on 754 records, yielding 27 articles. The final step was the full-text assessment, in which 23 records were excluded for various reasons. Therefore, four studies (Trachtman 2018 [27], Rheault 2023 [28], Heerspink 2023 [29], and Rovin 2023 [30]) were included in the quantitative and qualitative synthesis (Fig. 1).

Characteristics of included studies

All included RCTs evaluated the efficacy and safety of sparsentan compared to irbesartan in patients with FSGS or IgA nephropathy and were published between 2018 and 2023. Rovin 2023 [30] addresses the final analysis of kidney outcomes of Heerspink 2023 [29], which extended for two years. Interventional groups were treated with a target dose of sparsentan 800 mg/day orally in Trachtman 2018 and Rheault 2023 [27, 28], while in Heerspink 2023 [29], the target dose was 400 mg/day.

The comparator received irbesartan 300 mg/day. Immunosuppressive drugs were allowed to be continued in 2 studies [27, 28] while it was an exclusion criterion for participants involved in the third study [29]. There was a washout period of ARBs and ACELs for two weeks before randomization in two studies [27, 28] and just before the randomization in Heerspink 2023 [29]. The overall population is 884 patients with different types of glomerulonephritis (FSGS and IgA nephropathy). The baseline and study characteristics of the included studies are shown in Tables 1 and 2.

Risk of bias assessment

The included RCTs were assessed by ROB 2. All included studies were of high quality as they were considered at low risk of bias for all domains (Figure S1, 2).

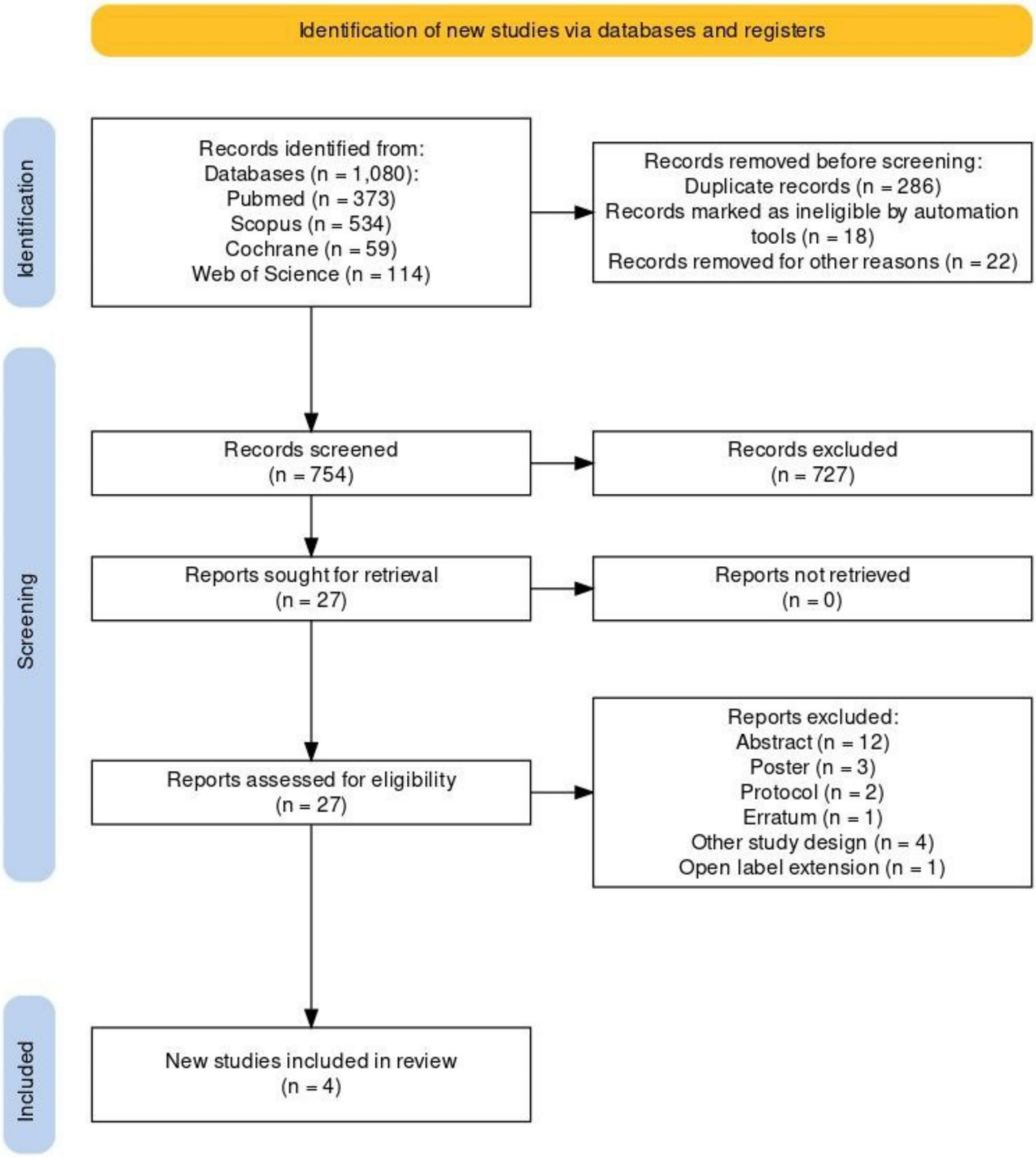

Fig. 1 PRISMA diagram of study selection process

Primary outcomes

Change of UP/C ratio from baseline

Changes in the UP/C ratio from the baseline were assessed based on 24-hour urine sample collection at the endpoint of each study. Pooled analysis showed that sparsentan significantly reduces UP/C ratio compared to irbesartan (ratio of percentage reduction = 0.66, 95% CI [0.58 to 0.74], $P < 0.000001$). Pooled studies were homogenous ($P = 0.36$, $I^2 = 2\%$) (Fig. 2).

Remission of proteinuria

Meta-analysis results revealed significantly higher rates of complete remission (RR = 2.57, 95% CI [1.73 to 3.81], $P < 0.00001$) and partial remission (RR = 1.63, 95% CI [1.4

Table 1 Summary of the characteristics of included RCTs

Study ID	Study Duration (Weeks)	Population	Interventions	Control	Sample Size		Efficacy outcomes assessed
					Intervention	Control	
Trachtman 2018[27]	8	Eligible patients were aged 8–75 years with FSGS	sequential dose-escalating of sparsentan once/d: cohort 1→ 200 mg cohort 2&3→400 mg cohort 4&5→800 mg	irbesartan 300 mg once daily	sparsentan (*n* = 73) cohort 1:2&3:4&5 (*n* = 13:23:34)	Placebo (*n* = 36)	- Reduction from baseline in UP/C - Complete (urinary protein excretion < 0·3 g/day) and partial (UP/C < 1·5) proteinuria remission. - Blood pressure (change from baseline) - eGFR (change from baseline) – 24-h urinary protein (changes from baseline)
Heerspink* 2023[29]	36	Adults with IgA nephropathy who continue to have persistent proteinuria despite receiving maximized treatment with (ACE) inhibitors or (ARBs).	sparsentan 400 mg once daily	irbesartan 300 mg once daily	Sparsentan (*n* = 202)	Placebo (*n* = 202)	- Reduction from baseline in UP/C - Complete (urinary protein excretion < 0·3 g/day) and partial (urinary protein excretion < 1·0 g/day) proteinuria remission. - Blood pressure (change from baseline) - eGFR (change from baseline) # - eGFR slope (total and chronic) # - Proportion of patients reaching composite kidney endpoint of confirmed 40% reduction in eGFR from baseline, kidney failure or all-cause mortality. - Change from baseline in urine albumin–creatinine ratio.
Rheault 2023[28]	112	Eligible patients were aged 8–75 years with FSGS	sparsentan (target dose, 800 mg once daily)	irbesartan (target dose, 300 mg once daily)	sparsentan (*n* = 184)	Placebo (*n* = 187)	- Reduction from baseline in UP/C - Complete (urinary protein excretion < 0·3 g/day) and partial (UP/C < 1·5) proteinuria remission. - Blood pressure (change from baseline) - eGFR (change from baseline) - eGFR slope (total and chronic) - Proportion of patients reaching composite kidney endpoint of confirmed 40% reduction in eGFR from baseline, kidney failure or all-cause mortality. - Proportion of patients reaching composite kidney endpoint of confirmed 40% reduction in eGFR from baseline, kidney failure or renal death. - Change from baseline in urine albumin–creatinine ratio.

FSGS: Focal segmental glomerulosclerosis; ACE: Angiotensin-converting enzyme inhibitors; ARBs: Angiotensin receptor blockers; UP/C: Urinary protein to creatinine ratio; eGFR: estimated glomerular filtration rate

*. Rovin 2023 is a two-year results study from Heerspink 2023, so they have the same study characteristics except the follow-up period, which is 110 weeks in Rovin 2023, and different reported outcomes

#: reported in the extension study (Rovin 2023)

to 1.91], $P<0.00001$) of proteinuria with sparsentan compared with irbesartan. Pooled studies were homogenous in both complete and partial remission ($P=0.97$, $I^2=0\%$), ($P=0.55$, $I^2=0\%$) respectively (Figs. 3 and 4).

Secondary outcomes

Change in eGFR from baseline

The pooled effect estimate did not favor either sparsentan or irbesartan (MD = 1.98 ml/min per 1.73mm2, 95% CI [-1.05 to 5.01], $P=0.2$). Pooled results showed mild heterogeneity ($P=0.12$, $I^2=52\%$). So, we conducted a sensitivity analysis to find that by removing Trachtman 2018, heterogeneity was resolved and results remained consistent (Figs. 5 and 6), and (Table S4).

The eGFR total and chronic slopes

The eGFR total slope was the slope from day 1 to week 108 [28] or 110 [30], while the eGFR chronic slope was the slope from week 6 to week 108 [28] or 110 [30]. These outcomes were evaluated only in two included studies and measured as ml/min per 1.73 mm^2 per year. The forest plot showed almost statistically significant difference in the eGFR total slope between sparsentan and irbesartan (MD = 0.87, 95% CI [-0.02 to 1.77], $P=0.05$). On the other hand, it was found that patients in the sparsentan group presented a GFR chronic slope significantly better (as the smaller the rate the lower the decline in the kidney function) with GFR values at last follow-up significantly higher compared to patients in the irbesartan

Table 2 Baseline characteristics of the included studies

Study ID		Trachtman 2018		Heerspink 2023		Rheault 2023		Rovin 2023	
Study arms		Sparsentan	Irbesartan	Sparsentan	Irbesartan	Sparsentan	Irbesartan	Sparsentan	Irbesartan
Sample Size		73	36	202	202	184	187	202	202
Age, mean ± SD		NR	NR	46.6 ± 12.8	45.4 ± 12.1	41.7 ± 16.5	41.5 ± 17.3	46.6 ± 12.8	46.6 ± 12.8
No. of adults (age ≥ 18 y)		60 (82)	26 (72)	202 (100)	202 (100)	168 (91.3)	168 (89.8)	202 (100)	202 (100)
Sex, Males n (%)		41 (56)	19 (53)	139 (69)	143 (71)	101 (54.9)	99 (52.9)	139 (69)	139 (69)
Ethnicity (Hispanic/Latino) n (%)		14 (19)	6 (17)	17 (8)	16 (8)	34 (18.5)	44 (23.5)	17 (8)	17 (8)
Race, n(%)	**Asian**	5 (7)	1(3)	67 (33)	49 (24)	23 (12.5)	67 (33)	67 (33)	48 (24)
	Black or African American	8 (11)	7 (19)	1 (< 1)	3 (1)	17 (9.2)	1 (< 1)	1 (< 1)	3 (1)
	White	57 (78)	26 (72)	130 (64)	142 (70)	137 (74.5)	130 (64)	130 (64)	142 (70)
	Other	3 (4)	2 (5.6)	4 (2)	9 (4)	10 (5.4)	4 (2)	4 (2)	9 (4)
eGFR, mL/min per 1·73 m mean ± SD		74.4 ± 37.3	74.5 ± 44.7	56·9 ± 24.4	57·1 ± 23.6	63.3 ± 28.6	64.1 ± 31.7	56·9 ± 24.4	56·9 ± 24.4
Urine protein–creatinine ratio g/g mean (CI)		3.61 (0.4–18.7)	3.12 (0.9–10.7)	1.3 (0·8–1·8)	1.2 (0·9–1·7)	3.1 (2.3–4.5)	3.0 (2.1–4.7)	1.3 (0·8–1·8)	1.3 (0·8–1·8)
Serum albumin, g/L mean ± SD		36.1± 5.8	35.4 ± 7.2	41·2 ± 3.9	41·7 ± 3.8	34.9 ± 7.4	34.9 ± 7.5	41·2 ± 3.9	41·2 ± 3.9
Blood pressure, (mmHg) mean ± SD	**systolic**	NR	NR	128 ± 14·4	130 ± 12·4	133 ± 15	128 ± 14·4	128 ± 14·4	
	diastolic	NR	NR	82 ± 10·6	83 ± 10·6	131 ± 15	82 ± 10·6	81.6± 10·6	83.2± 10·6
Patients receiving immunosuppressive n (%)		21 (29)	13 (36)	#	#	50 (27.2)	46 (24.6)	#	#
Patients receiving diuretics n (%)		26 (36)	9 (25)	39 (19.3)	39 (19.3)	68 (37)	73 (39)	39 (19.3)	39 (19.3)
***Patients receiving antihypertensive drugs*n (%)**		40 (55)	20 (56)	88 (44)	83 (41)	152 (82.6)	143 (76.5)	90 (45)	88 (44)

#: patients receiving immunosuppressive drugs for 2 weeks or more within 3 months before screening were excluded

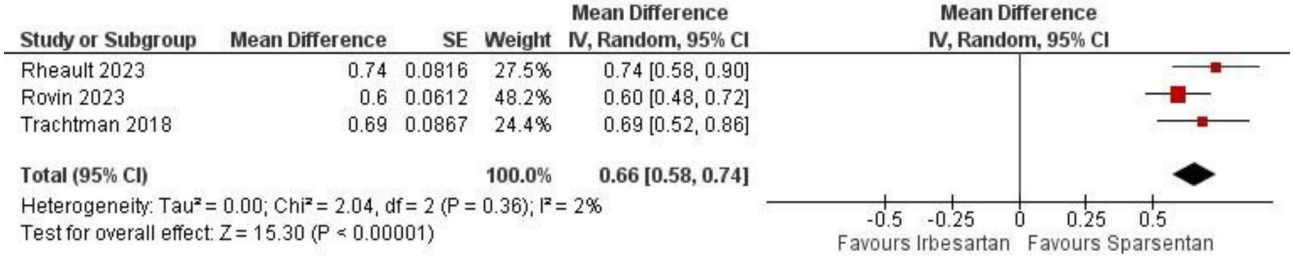

Fig. 2 Forest plot showing the change in UP/C ratio from baseline

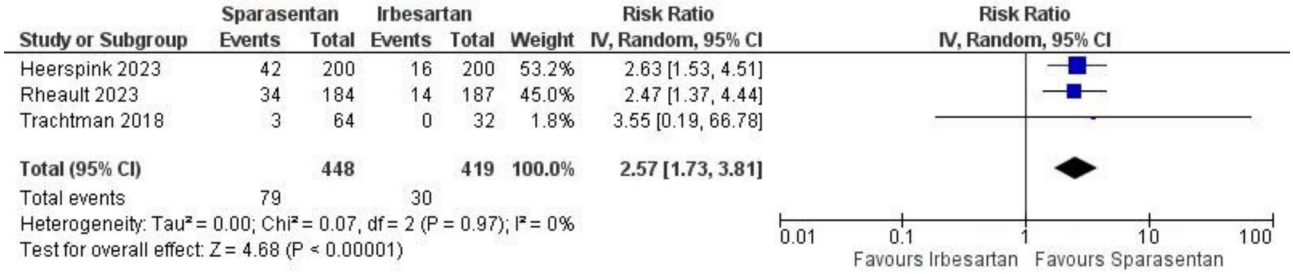

Fig. 3 Forest plot showing the percentage of patients achieving complete remission of proteinuria

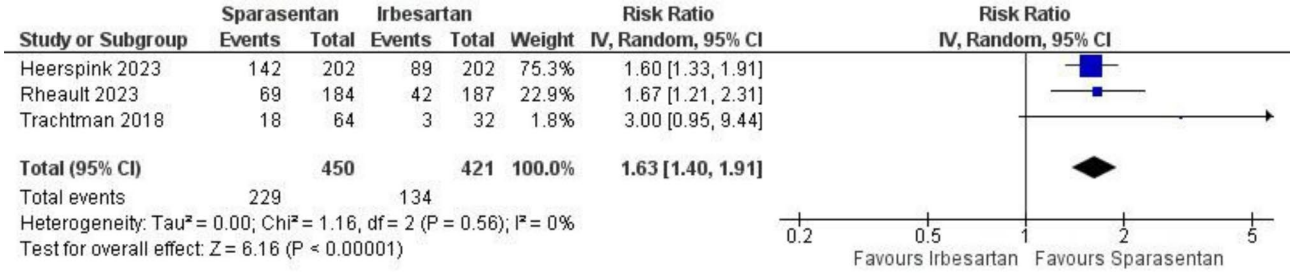

Fig. 4 Forest plot showing the percentage of patients achieving partial remission of proteinuria

group (MD=1.06, 95% CI [0.12 to 2.0], *P*=0.03). Pooled results were homogenous (*P*=0.56, I^2 =0%) and (*P*=0.87, I^2 =0%) respectively (Figure.S3, 4).

SBP and DBP

There was a statistically significant reduction of DBP in the sparsentan group compared to irbesartan (MD= -4.24 mmHg, 95% CI [-7.09 to -1.38], *P*=0.004). Pooled results had mild heterogeneity (*P*=0.18, I^2 =41%). On the contrary, its effect on SBP was insignificant, with mild heterogeneity. Thus, we conducted a sensitivity analysis to find that sparsentan had a statistical difference in the reduction of SBP in patients with FSGS compared to irbesartan (MD= -4.97 mmHg, 95% CI [-9.02 to -0.93], *P*=0.02); with homogenous pooled results (*P*=0.36, I^2 =0%) (Figure S5, 6) and (Table S4).

Composite kidney outcome

Composite kidney outcome is the confirmed reduction in eGFR of at least 50%, kidney failure, or death, and was assessed in two studies [28, 30]. The analysis did not show any statistically significant difference between sparsentan and irbesartan (RR=0.81, 95% CI [0.59 to 1.12], *P*=0.2); studies were homogenous (*P*=0.51, I^2 =0%) (Figure S7).

Safety outcomes

In the included studies, no significant differences in patients experiencing any treatment-emergent adverse events (TEAEs), serious TEAEs, TEAEs leading to study withdrawal or death, headache, nausea, dizziness, edema, diarrhea, and hyperkalemia were observed in different doses of sparsentan in comparison with irbesartan group (Figure.S8-18). Pooled studies were homogenous regarding all outcomes except for nausea (*P*=0.12, I^2 =53%). After conducting leave out one analysis and removing Rheault 20,223, heterogeneity was resolved (Table S5).

Furthermore, the results showed a statistically significant difference in hypotension /orthostatic hypotension outcome (RR=2.02, 95% CI [1.3 to 3.16], *P*=0.002) between the two groups with a higher rate of hypotension in the sparsentan group. Pooled studies were homogenous (*P*=0.32, I^2 =13%) (Figure.S16). A summary of the safety outcomes measures is found in Table S3.

Discussion

We found that sparsentan significantly reduces the UP/C ratio compared to irbesartan. Furthermore, we observed higher rates of both complete and partial remission of proteinuria with sparsentan. Notably, the eGFR chronic slope was statistically significantly higher in the sparsentan group, and there was a significant reduction in DBP compared to the irbesartan group. Despite these differences, both medications showed comparable results concerning the eGFR from baseline, the eGFR total slope, and the composite kidney outcome.

The evaluation of the efficacy of sparsentan in FSGS and IgA nephropathy is extensive and comprises many aspects that focus mainly on proteinuria and kidney function. The dual action of sparsentan on endothelial and angiotensin 2 receptors provides it an advantage over other antiproteinuric drugs in clinical and preclinical studies [30, 31]. We assessed the change of UP/C ratio from baseline because it is the strongest predictor of the rate of progression of renal disease and the development of renal failure in IgA nephropathy and FSGS [31]. Sparsentan showed a significant reduction in the UP/C ratio compared to irbesartan. Complete remission of the condition was defined as UP/C<0.3 g/g, while partial remission was defined as UP/C≤1.5 g/g and a>40% reduction in UP/C from baseline [31, 32]. The remission of proteinuria is considered an essential predictor of kidney function preservation. Patients in sparsentan groups revealed higher rates of both complete and partial remissions than patients in irbesartan groups. This remission warrants less risk of progressive kidney disease among those patients. Regarding blood pressure, sparsentan was superior to irbesartan in reducing DBP; however, its effect on SBP was insignificant compared to irbesartan. Heterogeneity was found in both outcomes and resolved by sensitivity analysis by removing Heerspink 2023. Sparsentan showed a marked reduction in SBP among FSGS groups compared to irbesartan.

Although data support the use of proteinuria reduction as a reasonably likely surrogate end point for a treatment's effect on progression to ESKD in IgA nephropathy [33] and FSGS [34], the best surrogate end points for kidney disease progression in clinical practice should

be: eGFR decline at different time points, time to ESKD, eGFR decline > 30% or 50% at different time points. The drug effect on the GFR decline should be considered the best surrogate end point, certainly much more important than the reduction of proteinuria. Changes in eGFR from baseline were analyzed to quantify the impacts of the two drugs on kidney function, which is one of the most important clinical tests that reflect the functional state of the kidneys [35]. We noticed that the difference in eGFR change between the two groups was insignificant. The results were heterogeneous and could be resolved through sensitivity analysis by excluding Trachtman 2018, which showed a dramatic change in the *p*-value (from 0.2 to 0.0008). This supports the idea that sparsentan has a long-term effect on preserving eGFR and kidney function. This justification was evidenced by analysis of the same outcome for Trachtman 2018 and Rovin 2023 at week 4, which showed a minimal effect of sparsentan when compared to irbesartan in the short term (Figure. S19). Moreover, when we noticed that the heterogeneity was resolved by excluding the Trachtman 2018, which had the highest eGFR at the baseline. Hence, we performed the meta-regression and found that the eGFR at the baseline may contributes to this heterogeneity (Table S6).

The eGFR slope representing the rate of change in eGFR per year was assessed because it is a good predictor of progression to kidney failure [36, 37]. The total eGFR slope results did not show marked differences between the two arms. In contrast, sparsentan improved chronic eGFR slope compared to irbesartan, indicating more preservation of kidney function. There was no significant difference between sparsentan and irbesartan regarding clinically relevant composite kidney endpoints. Concerning safety evaluation, none of the adverse events favored either of the two groups except hypotension, which occurred at higher rates in patients receiving sparsentan. This decrease in blood pressure guides us to consider that patients receiving additional antihypertensive drugs should be continuously monitored with dose titration [38].

Clinical implications

Individuals with FSGN and IgA nephropathy experiencing persistent proteinuria levels between 0.44 to < 0.88 g/g face an increased risk of progressive kidney disease [39]. The primary objective of managing these conditions is to maintain kidney function. The current standard treatment involves RAAS using either ACEI or ARB, administered at the highest tolerable or permissible dosage [40]. Furthermore, it is significant to highlight that several therapeutic attempts have been proposed in IgA nephropathy, with anti-endothelin antagonists being possible promising agents together with anti-APRIL and anti-BLyS/BAFF antibodies, and some complement inhibitors [41]. Despite optimal supportive care, approximately 50% of patients may still progress to kidney failure within 20 years, leading to reduced quality of life and increased risk of premature death [42]. However, sparsentan has demonstrated lower rates of proteinuria and higher rates of partial and complete remission of proteinuria, thereby preserving kidney function while maintaining a favorable safety profile.

Corticosteroids and other immunosuppressive agents may be employed to treat FSGN and IgA nephropathy. However, long-term use of steroids and immunosuppressive drugs carries a risk of serious adverse events such as increased risk of systemic infections due to immunosuppression with increasing risk of morbidity and mortality [43]. Sparsentan is an excellent alternative for managing FSGN and IgA nephropathy, as it does not impact the immune system, consequently reducing the risk of infections associated with immunosuppressive therapies [38].

Strength and limitations

In this systematic review and meta-analysis, we present the current knowledge on the efficacy and safety of sparsentan against irbesartan in FSGS and IgA nephropathy patients. It is the first systematic review and meta-analysis to assess the efficacy and safety of sparsentan versus ARBs in IgA nephropathy and FSGS patients. Campbell et al. referenced Trachtman 2018 in their review but did not integrate it into their analyses [44]. Additionally, their review specifically focused on assessing the efficacy and safety of ARBs and ACE inhibitors in patients diagnosed with primary FSGS only. It is worth noting that one ongoing phase II RCT evaluates the efficacy of sparsentan in pediatric patients with FSGS (NCT05003986), registered in August 2021. Moreover, a single-center phase II trial registered in December, 2020 (NCT04663204) is recruiting to determine the nephroprotective effects in newly diagnosed IgA nephropathy patients.

The current study has some limitations. Notably, there was a difference in the endpoint among the clinical trials included in the analysis. The analysis endpoint in Trachtman 2018 was after eight weeks and 112, 36, and 110 weeks in Rheault 2023, Heerspink 2023, and Rovin 2023, respectively. Fortunately, this discrepancy in endpoint did not cause heterogeneity except in eGFR, which was discussed before. Moreover, the number of available published RCTs was limited, which may limit the external validity of the results of this evidence. Another limitation was the absence of error bars in the figure of the diastolic blood pressure in Rheault 2023. To overcome this obstacle, we assumed equal variances similar to those of systolic blood pressure. There was unexplained heterogeneity in nausea outcomes. Also, the different

definitions of partial remission between the studies are worthy of mention; as in Trachtman 2018 and Rheault 2023, it was UP/C < 1.5, while in Heerspink 2023, it was urinary protein excretion < 1.0 g/day. Finally, we could not assess the publication bias using funnel-plot-based methods because they are inaccurate for fewer than ten studies reporting the same outcome.

Conclusion

In conclusion, Sparsentan was effective as an antiproteinuric treatment and showed higher rates of remissions of proteinuria in both IgA nephropathy and FSGS. However, it had relatively similar effects as irbesartan regarding kidney composite outcomes and total eGFR slope. The evidence of the short-term effects of sparsentan on eGFR and SBP is still inconclusive, and more trials are required. Sparsentan showed a good safety profile of all measured adverse events except for episodes of hypotension. Therefore, future RCTs comparing sparsentan against ACEIs, ARBs, corticosteroids, immunosuppressive drugs, and standard therapy are required to confirm its safety and efficacy in patients with FSGS and IgA nephropathy. Finally, further real-world studies are needed to clarify the effectiveness of sparsentan in managing IgA nephropathy and FSGS.

Supplementary Information

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Supplementary Material 1

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Author contributions
AAAE: conceptualization and methodology. AAAE, MAA, AME and AR: investigation and data curation. AME: formal analysis. AAAE, MAA, and AME: Writing - Original Draft. AR and RS: Supervision. AME: Project administration. AME, AR, MA, RS, and YA: Writing - Review & Editing. All authors reviewed the manuscript.

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Data availability
Data is provided within the manuscript or supplementary information files.

Declarations

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Not applicable.

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Conflict of interest
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Competing interests
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