Review Article

Sparsentan: Sparsentan- A novel, non-immunosuppressive, dual action angiotensin II and endothelin A receptor antagonist -A new hope for glomerular disease.

Gupta RD¹, Noman MU²

Correspondent: Dr. Ratan Das Gupta. Professor and Head, Department of Nephrology, Shaheed Suhrawardy Medical College. Mobile: 01711-101892

DOI: https://doi.org/10.3329/jssmc.v14i2.73180

Introduction
Sparsentan is an oral medication that blocks both Angiotensin Receptor Type 1 (AT1R) and Endothelin Receptor A (ETAR). It was created by merging the structural elements of irbesartan, an AT1R antagonist, and biphenylsulfonamide, an ETAR antagonist.¹ Sparsentan has similar affinity for both the receptor and it is the first drug in this class. In February 2023, the use of sparsentan to reduce proteinuria in adults with primary immunoglobulin A nephropathy (IgAN) at risk of rapid disease progression was approved by the FDA under accelerated approval based on reduction of proteinuria.²

Endothelin
Endothelin (ET) is a 21-aminoacid polypeptide described as the major vasoconstrictor of the organism. It is produced mainly by endothelial cells, but also by cells of the renal system, such as the epithelial and mesangial cells.³ The ET polypeptide is present in three isoforms: ET-1, ET-2 and ET-3, with ET-1 being the greatest vasoconstrictor and the only one found at the protein level in the kidney.³ Endothelin receptor A (ETA) and B (ETB). ETA is localized in vascular smooth muscle cells and presents more binding affinity for ET-1 and ET-2 than for ET-3, due to the differences in the amino acid sequences. ETA activation induces a robust vasoconstrictor response and promotes cell proliferation and accumulation of the extracellular matrix. In the kidney, ET has an essential role in blood flow and glomerular filtration regulation and in water–sodium and acid–base balances. ETA and ETB are expressed on the glomerular podocytes, mesangial cells and on the afferent and efferent arterioles. Regarding the tubular compartment, ETB is expressed in all the regions in the renal tubule while ETA is scarcely expressed on the proximal tubule and the descending Henle’s loop.⁴ In physiological conditions, ET-1 through ETA produces vasoconstriction of the afferent arteriole, reducing blood flow and, consequently, the glomerular filtration rate (GFR). Contrarily, the activation of ETB induces vasodilation, antiproliferative effects and ET-1 depuration.⁵⁶ In pathological conditions, such as diabetes or hypertension, the concentration of ET-1 is increased because of the hyperglycaemia, acidosis and the presence of insulin, angiotensin II and proinflammatory cytokines, which causes sustained vasoconstriction. This may contribute to deleterious effects such as hyperfiltration (mainly in early diabetic nephropathy or incipient obesity-related kidney disease⁶⁷⁺⁺ or podocyte damage and, eventually, proteinuria and GFR decline.⁸ The endothelin receptor antagonists (ERA) are postulated as a therapeutic strategy to reduce proteinuria and delay the progression of GFR decline.¹¹
Mechanism of renoprotection by Endothelin Receptor Antagonist

Endothelin receptor antagonist has clear effects on glomerular hemodynamics. ETA receptor antagonism improves blood pressure via vasodilatation and decreases proteinuria and the filtration fraction (ratio of glomerular filtration rate over renal plasma flow), providing renoprotective effects. Moreover, ETA receptor blockade may improve endothelium-dependent relaxation and vasomotion. Many studies have found a reduction in the podocyte injury, which lead to the stabilization of the glomerular and podocyte structure with the use of ETA. Mesangial cells produce ET-1, although in a much smaller proportion than endothelial cells. ET-1 produced by mesangial cells can act in an autocrine way by binding to ET receptors. Via ETA it results in the contraction of mesangial cells, cell proliferation and mesangial matrix accumulation. These deleterious effects can be blocked using ERAs. ET-1 can induce inflammation and fibrosis, ET-1 resulted in interstitial fibrosis in transgenic mice expressing human ET-125 that can be reversed only by ETA-selective receptor antagonists.

Pharmacokinetics

The pharmacokinetics of sparsentan are best described by a two-compartment model with first order absorption with lag time, dose-dependent bioavailability and first order elimination. Sparsentan displays time-dependent pharmacokinetics, potentially inducing its own metabolism over time. After multiple administrations of 400 mg once daily (recommended dosage), steady-state plasma concentrations are reached within 7 days, with no accumulation. At steady state with 400 mg once daily, half-life 9.6 h. Sparsentan should be taken before the morning or evening meal and the dosing pattern with respect to meals should be maintained. Age (18–73 years), sex, race, mild to moderate reduction in estimated glomerular filtration rate (eGFR; 30–89 mL/min/1.73 m2), or mild to moderate liver function impairment (Child-Pugh class A or B) had no clinically significant effect on sparsentan pharmacokinetics. The effects of severe liver function impairment (Child-Pugh class C) or eGFR < 30 mL/min/1.73 m2 have not been studied.

Randomized Control Trials in early years

The largest trials testing ERAs have been performed in type 2 diabetic patients (Table 1). In these studies, ERAs have shown to reduce albuminuria and slightly decrease blood pressure. The effect of selective endothelin antagonist on albuminuria is consistent across different studies, obtaining a 30–40% reduction on urine albumin-to-creatinine ratio (UACR) in the groups that received the active treatment. However, blood pressure reduction is moderate and shows different results between RCTs. In addition, the SONAR study showed that BP reduction is more evident when initiating the treatment and becomes milder after chronic treatment. Regarding GFR preservation, selective ERAs have displayed protective effects or no effect among the different RCTs performed to date. The SONAR trial, which treated responder patients (patients that showed a decrease in UACR of at least 30% with no substantial fluid retention during the enrichment period) for a median follow-up of 2.2 years, showed that 0.75 mg of atrasentan on top of the RAS blockade was able to preserve 0.65 mL/min/1.73 m2 of GFR and to prevent the doubling of serum creatinine during the treatment period.

Table 1: Randomized control trials in the initial years

ETA in IgAN

Sparsentan treatment of adults with IgAN is being assessed in the phase 3 PROTECT clinical trial. The trial randomized 404 patients with IgAN to sparsentan treatment versus the active comparator irbesartan with more than 95% titrated to maximal label irbesartan dose and managed under ideal study conditions, including full optimization of medication adherence. Eligible patients had proteinuria ≥1 g/day despite maximally tolerated RAASi that was at least one-half of the maximum labeled dose for ≥12 weeks at enrollment (median [interquartile range] urine protein/creatinine ratio [UP/C] was 1.2 [0.8–1.8] g/g for the 404 patients). The study
met its primary efficacy endpoint (prespecified interim analysis) of sparsentan-treated patients showing significantly greater reduction from baseline in UP/C at week 36 based on a 24-hour urine sample (primary analysis set)33 and the proteinuria reduction was maintained throughout the 2-year study period (sparsentan −42.8% geometric least-squares mean reduction of UP/C from baseline at week 110 vs irbesartan −4.4%).34 Greater proteinuria reduction with sparsentan versus irbesartan was consistent across patient subgroups of demographic (eg, age, sex, race) and baseline clinical characteristics (eg, estimated glomerular filtration rate [eGFR] and proteinuria levels). Rates of complete (urinary protein excretion <0.3 g/day; 31% vs 11% of patients) and partial (urinary protein excretion <1.0 g/day; 78% vs 53% of patients) proteinuria remission at any time and at each follow-up visit were higher with sparsentan versus irbesartan.34 The 2-year PROTECT trial supported preservation of kidney function with sparsentan treatment as shown in a slower rate of eGFR decline versus irbesartan.34

Treatment-emergent adverse events (TEAEs) in sparsentan-treated versus irbesartan-treated patients in the PROTECT trial of particular clinical relevance were hyperkalemia (16% vs 13%), peripheral edema (15% vs 12%), dizziness (15% vs 6%), hypotension (13% vs 4%), and anemia (8% vs 4%).40 There were no discontinuations due to heart failure or edema. Overall, the sparsentan safety outcomes in PROTECT were consistent with the DUPEX and DUET trials and long-term treatment during the DUET OLE in FSGS.35-38

In Phase 2, Open-Label, Single-Arm, Cohort Study to Evaluate the Safety, Efficacy, and Pharmacokinetics of Sparsentan Treatment in Pediatric Subjects With Selected Proteinuric Glomerular Diseases (EPPIK) study which was multicenter, open-label, 112-week study of sparsentan in approximately 57 pediatric subjects aged ≥ 1 year to <18 years with selected proteinuric glomerular diseases, divided into 2 populations, defined as follows: Population 1: Subjects with selected proteinuric glomerular diseases associated with Focal Segmental Glomerulosclerosis (FSGS) and Minimal Change Disease (MCD) histological patterns, Population 2: Subjects with kidney biopsy-confirmed immunoglobulin A nephropathy (IgAN), immunoglobulin A vasculitis (IgAV), or subjects with Alport syndrome (AS) evaluating long-term safety, tolerability, and efficacy with pharmacokinetic evaluations at Day 1 (Baseline), Day 2 (Visit 4), and Week 12 (Visit 9). For each population, subjects will be enrolled in 3 cohorts based on age ranges. The study result is yet to be published.39

Summary of Sparsentan in IgAN: An alternative nonimmunosuppressive therapy in patients at high risk of chronic kidney disease progression (eg, urine protein-to-creatinine ratio of ≥1.5 g/g) despite receiving optimized therapy (eg, maximally tolerated angiotensin converting enzyme [ACE] inhibitors or angiotensin receptor blockers [ARBs]) for at least 3 to 6 months.32,40

**ETA in FSGS**

Sparsentan has been investigated in healthy volunteers (phase I studies) as well as in patients with primary or genetic FSGS (phase II DUET37 and phase III DUPEX41 studies). The phase II DUET study compared sparsentan (200, 400, or 800 mg/day) to irbesartan (300 mg/day) over 8 weeks.37 Patients treated with sparsentan had a higher reduction in urinary protein to creatinine ratio (UP/C) and had higher rates of patients reaching the FSGS partial remission end point (FPRE).37, 41 The ongoing phase III DUPEX study is investigating sparsentan treatment (400 mg/day for 2 weeks, titrating up to 800 mg/day) compared with irbesartan treatment (150 mg/day, titrating up to 300 mg/day) over 108 weeks.42 The primary end point of the DUPEX study is estimated glomerular filtration rate slope from week 6 to week 108, and the prespecified interim surrogate end point is the proportion of patients achieving FPRE (UP/C ≤1.5 g/g and >40% reduction in UP/C) at week 36.42 Interim results showed that sparsentan treatment led to significantly greater FPRE response compared to irbesartan.42 A population pharmacokinetic (PK) analysis was conducted and reported to characterize the PKs of sparsentan in healthy volunteers and patients with primary or genetic FSGS and to evaluate the impact of FSGS disease characteristics and concomitant medications on sparsentan PKs. Patients treated with sparsentan reach an FSGS partial remission end point at higher rates than with the current standard-of-care treatment, irbesartan.42

**ETA in Alport’s Syndrome**

Theactivation of ETAR has an important role in renal and inner ear pathologies in patients with AS. Despite being standard of care in patients with AS, the use of RAAsi does not mitigate the impact on hearing. Sparsentan, a dual ETAR/AT1R inhibitor, was able to extend
lifespan in AS mice and lead to greater reductions in proteinuria compared to a selective AT1R inhibitor (losartan) or selective ETAR inhibitor (atrasentan) when treatment was initiated at 4 weeks. Preventive use of sparsentan was also able to mitigate the structural and functional auditory changes in AS mice. This auditory benefit was not observed with losartan.43

Prescribing information44

Oral: 200 mg once daily for 14 days, then increase to target dose of 400 mg once daily if tolerated. Interruption of therapy: Consider restarting at 200 mg once daily after a treatment interruption. After 14 days, increase to target dose of 400 mg once daily if tolerated. Dosage adjustment for concomitant therapy: Significant drug interactions exist, requiring dose/frequency adjustment or avoidance.

Toxicity

Hepatotoxicity

Some endothelin receptor antagonists have caused elevations of aminotransferases, hepatotoxicity, and liver failure. In clinical studies, elevations in aminotransfases (ALT or AST) of at least 3 × the ULN have been observed in up to 2.5% of sparsentan-treated patients, including cases confirmed with rechallenge. Measure transaminases and bilirubin before initiating treatment and monthly for the first 12 months, and then every 3 months during treatment. Interrupt treatment and closely monitor patients who develop aminotransferase elevations more than 3 × ULN. Sparsentan should generally be avoided in patients with elevated aminotransferases (>3 × ULN) at baseline because monitoring for hepatotoxicity may be more difficult and these patients may be at increased risk for serious hepatotoxicity.

Embryo-fetal toxicity

Sparsentan can cause major birth defects if used by pregnant patients based on animal data. Therefore, pregnancy testing is required before the initiation of treatment, during treatment, and 1 month after discontinuation of treatment with sparsentan. Patients who can become pregnant must use effective contraception before the initiation of treatment, during treatment, and for 1 month after discontinuation of treatment with sparsentan.

Adverse Reactions

The following adverse drug reactions and incidences are derived from product labeling unless otherwise specified.

>10%:

Cardiovascular: Hypotension (14%; including orthostatic hypotension), peripheral edema (14%)

Endocrine & metabolic: Hyperkalemia (13%)

Nervous system: Dizziness (13%)

1% to 10%:

Hematologic & oncologic: Anemia (5%)

Hepatic: Increased serum transaminases (3%; including increased serum alanine aminotransferase and increased serum aspartate aminotransferase >3 × ULN)

Renal: Acute kidney injury (4%)

Authors:

1. Dr. Ratan Das Gupta.
   Professor and Head, Department of Nephrology, Shaheed
   Suhrawardy Medical College.
2. Dr. Meshah Uddin Noman,
   Associate Professor. Nephrology. OSD, DGHS, Mohakhali, Dhaka

Reference


of them on a single agent are very common and the most common antiepileptics. A gradual reduction of blood pressure should be performed if the precipitating factor is important to achieve favorized. In this case, the patient developed repeated generalized abnormalities including confusion and diminished consciousness. This indicates status epilepticus.


