Sparsentan – a dual antagonist - literature review on endothelin and endothelin antagonists

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The endothelin (ET) family consist of three 21 – amino-acid peptides (ET-1, ET-2 and ET-3). The most biologically relevant is ET-1. Endothelin acts by binding to two receptors- ET_A and ET_B. ET system plays an important role in human physiology by modulating total and regional blood flow, GFR, sodium and water secretion, acid-base handling by the kidneys. The pathologic effects of ET-1 in the kidney are largely mediated by activation of the ET_A receptor which promotes renal cell injury, proliferation of mesangial cells, vascular remodeling, proteinuria, inflammation, hypertrophy and development of renal fibrosis. Endothelin receptor antagonists' (ERAs) therapeutic potential was studied in many pathological conditions including kidney diseases. Several large studies demonstrated beneficial effects of ERAs in diabetic nephropathy on top of the renin-angiotensin-aldosterone system (RAAS) antagonists. The results of preclinical and early clinical studies of combined ERA and RAAS inhibitors led to development of a dual antagonist - sparsentan, which is presently evaluated in phase 3 clinical trials.

(NEPHROL DIAL POL. 2021; 25: 77-82)

Key words:
- endothelin
- endothelin receptor antagonists
- renin-angiotensin-aldosterone system antagonists
- sparsentan

Authors' contributions:
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Michał Nowicki – 1, 6
1. Conception and design
2. Data collection
3. Data analysis and interpretation, including statistical analysis
4. Manuscript preparation
5. Literature review
6. Critical evaluation and acceptance of the manuscript.

Endothelin

The history of endothelin dates back to 1988. It was discovered as an endothelium cell-derived peptide with a higher vasoconstrictive effect than any other substance, 10 times more potent than angiotensin II [1-2].

The endothelin (ET) family consists of three 21-amino-acid peptides (ET-1, ET-2 and ET-3). All of them are expressed in the human kidney. The main member is ET-1, which is biologically the most relevant isoform of three endothelins [3]. ET-1 peptide is produced by and acts upon every cell type in the body, especially vascular and airway endothelium, smooth muscle cells, macrophages, fibroblasts, cardiac myocytes, mesangial cells, podocytes and brain neurons [4].

Endothelin binds to two receptors- ET_A and ET_B, that were cloned in the early 1990s [5]. ET_A causes vasoconstriction, inflammation, cell proliferation, fibrosis and matrix accumulation, ET_B promotes vasodilation via nitric oxide and prostaglandin release, antiproliferative and antifibrotic effect [6-8]. Identification of these receptors allowed the development of an orally active antagonists [5].

The first ET_A receptor antagonist-BQ123 was developed in 1992 but has never been approved for human use. Bosentan, which was discovered in 1993, was the first endothelin receptor antagonist approved by the Food and Drug Administration (FDA) for the treatment of pulmonary arterial hypertension (PAH) [8]. Endothelin receptor antagonists (ERAs) have been in clinical use for two decades now in patients with PAH. The latest ERAs reviewed and approved by FDA in PAH were ambrisentam and macitentan [4].

During the last 30 years since the ERAs were discovered, numerous clinical studies investigating this class of drugs have been conducted in various indications i.e.: cardiac, renal, pulmonary diseases, cancer and immune disorders [4, 8].

Endothelin and the kidney

Endothelins are synthetized by almost every cell type in the kidney. Numerous ET receptors were found especially in the vasculature and medulla, which causes up to 10-fold greater sensitivity to the vascular effects of ET-1 than other organs' vascular beds. Thereby the ET system can modulate total and regional blood flow, glomerular filtration, sodium and water secretion, and acid-base balance in the kidneys [1, 5].

ET-1 is the most biologically relevant endothelin to the kidney physiology. The production of renal ET-1 is increased under conditions associated with renal disease progression. The factors increasing production of renal ET-1 are depicted in Figure 1 [5, 7].

The pathologic effects of ET-1 in the kidney are largely mediated by the activation of the ET_A receptor. By binding to ET_A receptors, ET-1 promotes renal cell injury, proliferation of mesangial cells, vascular remodeling, proteinuria, inflammation, hypertrophy and development of renal fibrosis [7].

ET_B receptors activation lowers blood pressure by promoting natriuresis and diuresis by directly inhibiting the reabsorption of sodium and water in the nephron [6, 8] which suggest that an ET_A selective antagonist could have more beneficial effects than the mixed ET_A and ET_B antagonism in kidney diseases [3]. The balance between ET_A and ET_B receptor activation may determine the effects of ET-1 within the kidney, especially in disease conditions [6].

Renal ET activity also affects the podocytes. Podocytes produce ET-1 and

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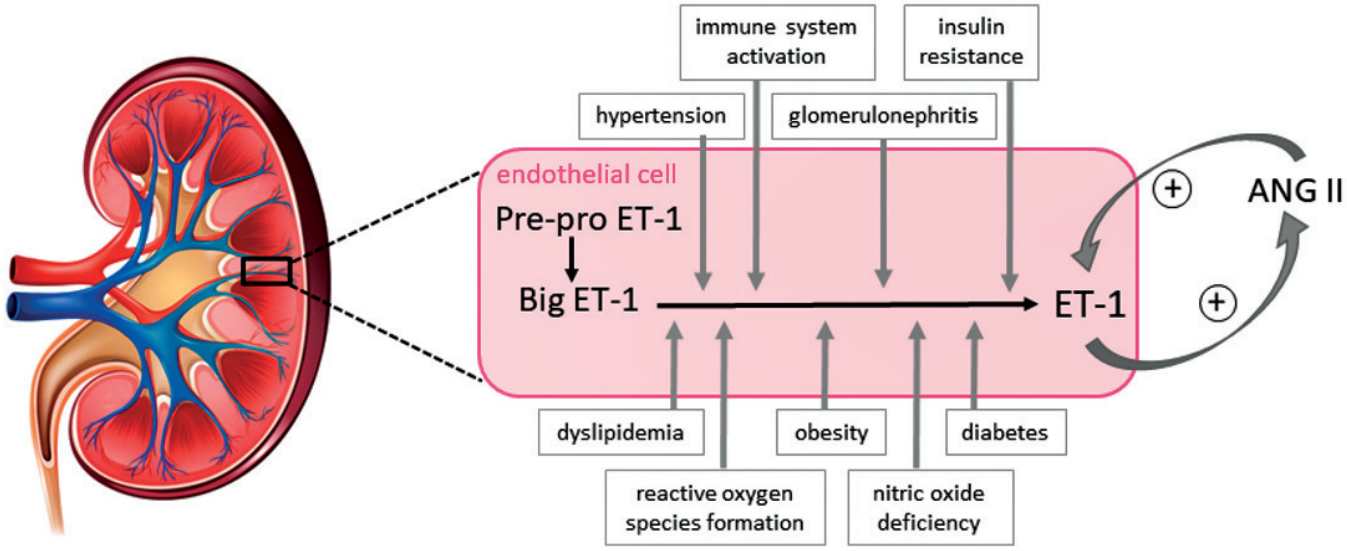

Figure 1
Factors that increasing the production of renal ET-1. ET – 1 – endothelin-1, ANG II – angiotensin II
Based on [5, 7]

express both ET_A and ET_B receptors. Activation of ET_A receptors promotes podocyte injury which results in dysfunction of the glomerular filtration barrier what may lead to proteinuric renal disease and the development of glomerulosclerosis. Increased albuminuria is an early sign of glomerular injury. The mechanism of the glomerular damage is not fully known and is likely to be multifactorial. The data shows that it can be due to a direct effect of ET_A receptors which increase a glomerular permeability to albumin. Blockade of ET_A receptors can prevent and reverse podocyte injury and actin cytoskeleton disruption [6-8].

Clinical trials assessing ERAs potential

The first pre-clinical study of ERAs was published in 1993. Benigini et al. created the rat model of renal mass reduction with hypertensive nephropathy and the experimental animals were treated by selective ET_A receptor antagonist. The study showed a reduction of proteinuria, limitation of glomerular injury and prevention of renal function deterioration [9]. Since then a growing pre-clinical and clinical evidence of ERAs potential as anti-proteinuric drugs with an advantageous impact on podocytes has been gathered [5].

The aging in humans progressively impairs renal function and structure and can be associated with spontaneous development of focal segmental glomerulosclerosis (FSGS). FSGS is widely varying, clinicopathological entity characterized by podocyte injury and hypertrophy, glomerular enlargement and glomerulosclerosis. The patients with FSGS present with a variable degree of proteinuria often of nephrotic range [5, 7]. The expression of ET-1 increases in the aging kidney even in the absence of the other risk factors. Ortmann et al. investigated the effect of treatment with ET_A receptor antagonist darusentan on renal structure and function in aged rats with established glomerulosclerosis and podocyte injury. Their study showed the substantial reduction of glomerulosclerosis and proteinuria, reversal of podocyte injury and glomerular basement hypertrophy [10].

Many experimental studies demonstrated beneficial effects of ERAs therapy in diabetic nephropathy. This therapeutic area appears to be the most relevant target of the ERAs since diabetes remains the main cause of chronic kidney disease (CKD). Hyperglycemia is a strong inducer of ET-1 production and together with ET-1 contribute to the disassembly of the actin cytoskeleton, apoptosis and podocyte depletion [5, 7].

Wenzel et al. conduced a randomized, placebo-controlled, double blind, parallel-design, dosage-range study of the effect of avosentan (ET_A selective receptor antagonist) on the urinary albumin excretion rate (UAER) in the patients with diabetic nephropathy. Avosentan was added to standard ACEI/ARB treatment. Avosentan decreased UAER compared to placebo in a full range of its doses. That was the first study which showed the combined effect of an ET_A and renin-angiotensin-aldosterone system (RAAS) antagonist. The study showed that the addition of ERAs to a standard nephroprotective therapy may have additional benefits in treatment of progressive diabetic nephropathy [11].

Kohan et al. investigated the effect of atrasentan, a selective ET_A receptor antagonist in patients with diabetic nephropathy treated with stable doses of RAAS inhibitor. Eighty-nine patients with a urinary albumin-to-creatinine ratio (UACR) of 100 to 3000 mg/g were randomized to placebo or atrasentan (0.25 mg, 0.75 mg or 1.75 mg daily) for 8 weeks. The study showed that atrasentan significantly reduced UACR only in the groups receiving 0.75 mg/d and 1.75 mg/d of atrasentan, and, interestingly, the greatest effect on albuminuria was noticed in the mid-dose group (0.75 mg/d). Simultaneously, this dose was associated with a relatively low rate of the development of the peripheral oedema, which has appeared as the most important side effect of ERAs [9].

The study conducted by de Zeeuw et al. also examined the effect of atrasentan in patients with diabetic nephropathy. Two hundred and eleven patients with albumin-to-creatinine ratio of 300-3500 mg/g treated with RAAS inhibitor were randomized to placebo or to 0.75 mg/d or 1.25 mg/d of atrasentan for 12 weeks. Compared to placebo both doses of atrasentan reduced albuminuria by about 40%. Moreover, in both groups a significant decreases in blood pressure (BP), low-density lipoprotein (LDL) cholesterol and triglyceride levels were noticed [12].

The phase 3 trial conducted by J. F. E. Mann et al. assessed the effect of avosentan in addition to continued RAAS inhibitor treatment on a combined endpoint including the time to doubling of serum creatinine, end stage renal disease or death in patients with type 2 diabetes mellitus and diabetic nephropathy. The study showed that avosentan significantly reduced the albumin-to-creatinine ratio, however the serious adverse effect such as fluid retention and a three-fold increase of congestive heart failure incidence caused the study early termination [13]. After the premature termination of the trial Hoekman et al. decided to identify risk markers of the congestive heart failure (CHF) after the treatment with avosentan. The analysis showed that the body mass increase in avosentan treated patients is the best early clinical indicator of fluid retention and subsequent risk of CHF development. The risk of CHF was higher in patients with lower serum LDL cholesterol, higher eGFR and in patients treated with statins. The

mechanism of fluid retention has not been fully elucidated. It may be associated with a low selectivity of ET_A receptor antagonism and ability to block ET_B receptor by avosentan especially in higher doses (50 mg/d) [11, 14].

These observations were very important in understanding risk-benefit profile of ERAs. It showed that lower doses of ERAs and use more selective ET_A receptor antagonists may confer the nephroprotection without inducing a life-threatening fluid retention.

The main clinical concern associated with ERAs are dose-related oedemas. Moreover, ERAs may induce headache, angioedema, hypotension and sulfonamide-based ERAs may cause hepatotoxicity. ERAs, similar to RAAS inhibitors are teratogenic [1, 7, 9].

Interactions of endothelin and the renin-angiotensin-aldosterone systems

The ET and RAAS components are highly vasoactive peptides with several direct interactions. Main effectors of RAAS are angiotensin II (ANG II) and aldosterone. Some effects of RAAS effectors, especially of ANG II are similar to ET-1 renal actions. ANG II mainly acts by AT_1 receptors and works on all renal cell types causing vasoconstriction, cell growth, extracellular matrix production and podocyte injury. What is important, the ET-1 increases the formation of ANG II by increasing the activity of angiotensin-converting enzyme and ANG II activates renal ET-1 production, which creates the vasoconstrictor positive feedback loop [1, 5, 15-17].

Podocytes express receptors for both angiotensin II and endothelin. ANG II increases glomerular permeability for albumin and causes podocyte actin cytoskeleton disruption and podocyte apoptosis. Similar effects are observed in podocytes during the endothelin exposure. ET-1 plays a specific role in podocyte cytoskeleton rearrangement resulting in foot processes obliteration, which is a hallmark of podocytopathies [5, 16, 17]. ERAs have beneficial effect on podocyte function which is essential for maintaining the glomerular filtration barrier. It is a key mechanism by which inhibition of ET_A receptor ameliorates renal structure and function [5].

Dual therapy for the first time was studied by Benigni et al. In 1998 the researchers presented the result of a combined blockage of ANG II and ET-1 receptors in a rat model of passive Heymann nephritis (PHN). The rats were treated by ET_A receptor antagonist LU-135252 or ACE-inhibitor trandolapril or both of the drugs for eight months. The combination treatment showed a significant reduction of proteinuria compared to treatment with each drug in a monotherapy. The combination therapy decreased serum creatinine and attenuated the development of glomerulosclerosis. These results proved that the dual therapy provides an additive nephroprotective effect [18].

Sparsentan

Sparsentan is a novel therapeutic strategy which combines two vasoconstrictor targets. The synthesis of dual AT_1 and ET_A receptor antagonist was based on structural similarities between irbesartan and some ET_A receptor antagonists. The idea of combining the structural elements of these two antagonists has led to the discovery of the dual action receptor antagonists (DARA) [17].

Sparsentan is a first-in-class, orally active antagonist that combines AT_1 and ET_A receptor antagonism in a single molecule and has similar high affinity to both receptors: 0,8 nm for AT_1 and 9,3 nm for ET_A [19]. Sparsentan has been granted the Orphan Drug Designation for the treatment of FSGS by the U.S. Food and Drug Administration and European Commission in 2015 [20]. The Retrophin Company (presently Traverse Therapeutics) decided to initiate a clinical trial program to assess the effect of a dual inhibition sparsentan in primary FSGS. Clinical trials conducted to assess efficacy and safety of sparsentan in different glomerulopathies are summarized in Table 1.

FSGS is described as a histopathological pattern of glomerular injury, which is caused by heterogenous group of clinical entities with a different mechanism of podocyte injury. There are four main forms of FSGS: presumed permeability factor-related FSGS (traditionally termed as 'primary FSGS'), secondary, genetic and FSGS of unknown cause [21-22]. Primary FSGS is supposed to be caused by circulating permeability factor which leads to a fast and global podocytopathy with a sudden clinical onset manifesting as the nephrotic syndrome in more than 70% of cases [22].

FSGS beside diabetes and arterial hypertension is one of the main causes of progressive glomerular diseases leading to chronic kidney disease requiring the renal replacement therapy. It is an underappreciated clinical condition and therefore there is a great need to introduce new therapeutic strategies [21]. The researchers of DUET study focused on a non-immunosuppressive therapy aiming at the reduction of proteinuria [15, 23]. Reduction of proteinuria is associated with a decreased risk of progression to ESRD [24-25].

Table 1
Clinical trials on sparsentan. (https://clinicaltrials.gov/ct2/results?cond=&term=sparsentan&cntry=&state=&city=&dist=, access 15/09/2021)
FSGS- Focal segmental glomerulosclerosis, UP/C- urinary protein-to-creatinine ratio, FPRE- FSGS partial remission of proteinuria endpoint defined as UP/C reduction up by >40% and UP/C ≤1.5 g/g
Based on [26, 29, 31-33, 40]

Name of the study	*DUET study*	*DUPLEX study*	*PROTECT study*
Phase	2	3	3
Disease	FSGS	FSGS	IgA nephropathy
Treatment	Sparsentan 200, 400, 800 mg/day Irbesartan 300 mg/day	Sparsentan 800 mg/day Irbesartan 300 mg/day	Sparsentan 400 mg/day Irbesartan 300 mg/day
Duration	144 weeks (8 weeks of double-blind treatment period, 136 weeks of open-label period)	108 weeks of double-blind treatment period	270 weeks (114 weeks of double-blind period, 156 weeks of open-label period)
Study group	109 patients	371 patients	380 patients
Outcome	Results of 8 weeks double-blind treatment period: 1) 45% vs 19% of UP/C reduction in sparsentan vs irbesartan group (p=0.006) 2) 28.1% vs 9.4% of patients achieved FPRE with sparsentan vs irbesartan group (p=0.04) Results of 76 weeks of open-label period: Up to 60% patients receiving sparsentan for 84 weeks achieved FPRE	Preliminary results after 36 weeks of treatment: 42.0% vs 26.0% of patients achieved FPRE with sparsentan vs irbesartan group (p=0.0094)	Preliminary results after 36 weeks of treatment: 49.8% vs 15.1% of proteinuria reduction with sparsentan vs irbesartan group (p<0.0001)

DUET study

DUET study is a phase 2, randomized, double-blind, active-control, dose-escalation study of the efficacy and safety of sparsentan compared to angiotensin II type 1 receptor antagonist irbesartan, in reduction of proteinuria in patients with primary FSGS.

One hundred and nine patients aged 8-75 years were included in the study The patients had biopsy proven FSGS or disease-causing genetic mutation associated with FSGS and baseline eGFR > 30 ml/min per 1.73 m^2 and urinary protein-to-creatinine ratio (UP/C) ≥1.0 g/g. The patients after 2 weeks washout of RAAS inhibitor were randomly divided to receive either sparsentan (200 mg, 400 mg or 800 mg daily) or irbesartan (300 mg daily) as an active control. The double-blind treatment period lasted 8 weeks and it was followed by open-label treatment with sparsentan (136 weeks) to assess its long-term safety [26].

During an 8-week of double-blind treatment the patients receiving sparsentan demonstrated greater than two-fold reduction in proteinuria compared to the irbesartan-treated patients. Sparsentan-treated patients presented also a greater reduction in urinary protein-to-creatinine ratio (UP/C) than irbesartan-treated (45% vs 19%; p=0.006), mostly in higher-dose sparsentan groups (400 mg/day and 800 mg/day). The FSGS partial remission of proteinuria endpoint (FPRE) defined as UP/C reduction by >40% to a value ≤1.5 g/g [27] was achieved by 28.1% of sparsentan-treated patients and 9.4% of irbesartan-treated patients (p=0.04). Treatment with sparsentan also induced a greater effect on blood pressure than irbesartan that may partially explain the difference in the effects of the study drugs on proteinuria. The eGFR, serum concentration of albumin and creatinine, liver function tests remained stable for sparsentan and irbesartan treated patients. The overall incidence of side effects was similar in sparsentan and irbesartan groups. However, sparsentan-treated patients more often reported hypotension, dizziness, oedemas, vomiting, diarrhea and nausea. There was no significant change in body mass or N-terminal pro-B-type natriuretic peptide level [28]. The data from 76-week open-label treatment period showed further reduction in UP/C and an increase of percentage of patients achieving FPRE (up to 60% in patients receiving sparsentan for 84 weeks). Sparsentan was generally well tolerated during the open-label extension period [29].

The favorable results of the DUET study encouraged the Retrophin Company to continue the development of sparsentan in FSGS (DUPLEX study). In addition, they provided the basis for evaluating the potential benefits of sparsentan in other glomerular diseases including IgA nephropathy (PROTECT study).

DUPLEX study

The DUPLEX study is an ongoing phase 3, double-blind, active-controlled, randomized study which compares sparsentan versus irbesartan and estimates their long-term impact on proteinuria, nephroprotective potential and safety profile in patients with FSGS. It is the largest interventional study to date in FSGS. The study enrolled 371 patients aged 8 to 75 years with UP/C ≥ 1.5 g/g, eGFR ≥ 30 ml/min per 1.73 m^2 at screening and biopsy – proven FSGS or genetic mutation in a podocyte protein associated with FSGS [30-31].

After two weeks washout from RAAS inhibitors the patients were randomly allocated 1:1 to receive sparsentan or irbesartan as an active control. The double-blind treatment period lasted 108 weeks and included a dose titration to a target dose of 800 mg of sparsentan or 300 mg of irbesartan daily. The primary efficacy endpoint is the assessment of the slope of eGFR rate from week 6 to week 108 in both treatment groups. The surrogate efficacy endpoint evaluate the proportion of patients achieving FPRE at 36 week. FPRE is described as strong predictor of renal survival in primary FSGS [30-31]. The data from interim analyses of the first 190 patients reaching 36 weeks of treatment showed that 42.0% of sparsentan-treated patients achieved FPRE compared to 26.0% of irbesartan-treated patients which is a highly significant effect (p=0.0094) [32].

PROTECT study

The ongoing PROTECT study is a phase 3, randomized, double-blind, international, active-controlled study that will assess safety and tolerability of sparsentan and evaluate long-term effects on sparsentan versus irbesartan on proteinuria and kidney function in patients with IgA nephropathy (IgAN) [33].

IgAN is the most prevalent primary glomerular disease globally. It was originally described by Dr. Jean Berger in 1968 and is also known as Berger's disease. IgAN is one of the leading causes of CKD and renal failure. It is characterized by mesangial IgA deposits in the glomeruli. The spectrum of clinical presentation is wide, from asymptomatic recurrent microscopic hematuria to rapidly progressive glomerulonephritis. The most common is proteinuria, microscopic hematuria with or without kidney failure [34-35]. Despite 50 years since the IgAN was discovered there is still no specific treatment [36]. In 2021 FDA granted the Orphan Drug Designation to sparsentan for the treatment of IgA nephropathy [37].

Three hundred and eighty patients with IgAN ≥ 18 years old with a persistent overt proteinuria and high risk of progression to renal failure despite a stable dose of RAAS inhibitor with urine total protein ≥1.0 g/day and eGFR ≥30 ml/min/1.73 m^2 at screening were enrolled to the PROTECT study. Patients were randomized 1:1 to sparsentan (initial dose 200 mg/day; target dose 400 mg/day) or an active control irbesartan (initial dose 150 mg/day; target dose 300 mg/day) [38]. The study consisted of 114-week double-blind period with the following open-label extension period for up to 156 weeks with a total duration of up to 270 weeks. The primary efficacy endpoint was the change in proteinuria at week 36 from baseline. Secondary efficacy endpoints assess the rate of change in eGFR over a 52 week and 104 week periods following the initial 6 weeks of randomized therapy [33, 39].

The interim data has been released recently by Traverse Therapeutics after 36 weeks of treatment are promising. Sparsentan-treated patients achieved 49.8% reduction in proteinuria compared to 15.1% reduction in proteinuria in irbesartan-treated patients (p<0.0001). The preliminary results show that to date sparsentan has been generally well - tolerated [40].

Sparsentan trials in recruiting status

Currently two new studies of sparsentan are enrolling patients [41]. The first one is a single centre, open-label, single-group study of the safety and activity of sparsentan in patients with biopsy-proven IgAN. Patients with no history of RAAS inhibitors therapy will be treated with sparsentan for 110 weeks to assess its nephroprotective potential [42]. The second one is a phase 2, multicenter, open-label study assessing efficacy, tolerability and antiproteinuric effect of sparsentan over the 108 – week treatment period. The study is designed for the pediatric population and includes children with selected proteinuric glomerular diseases such as: FSGS, Minimal Change Disease, IgAN, Immunoglobulin A-Associated Vasculitis and Alport Syndrome [43].

Conclusions

The discovery of endothelin more than three decades ago represented a major step in the understanding of human physiology and pathophysiology. Endothelin action is largely controlled by the kidney, which contains an abundant number of receptors. An increase in ET-1 levels in pathological conditions has been implicated in the mechanisms of kidney damage through the activation of ET_A receptor leading to proteinuria and chronic kidney disease.

The awareness of the important role of proteinuria in progressive kidney damage led to a search for new therapies. The studies showed that ERAs effectively reduce proteinuria in patients with on a stable treatment with the inhibitors of the renin-angiotensin-aldosterone system. What is more, the treatment with an ET_A receptor antagonists caused a reversal of podocyte injury and glomerular basement hypertrophy suggesting a long-lasting nephroprotective effects.

However, the research on ERAs has been hindered by a dose-related risk of fluid accumulation and its potential detrimental consequences including worsening or new-onset heart failure. However, the results of clinical trials show that these effects are usually mild and responsive to diuretics. It is important to use an appropriate dose, carefully select patients,

especially excluding those at high risk for developing congestive heart failure. It might also be considered to use diuretics as prevention of fluid accumulation.

ET_A receptor antagonists emerged as promising therapies that can intensify effects of the conventional nephroprotective therapies. The novel strategy which combines two vasoconstrictor targets RAAS and ET has become the focus of intensive clinical research. Favorable initial treatment effects with a combined ERAs and RAAS inhibitors therapy led to the development of a dual antagonist sparsentan. In the phase 2 DUET study this drug provided more than two-fold larger reduction of proteinuria compared to irbesartan. The findings from DUET study encouraged the researchers to further evaluate sparsentan in several ongoing trials.

The ongoing PROTECT and DUPLEX phase 3 studies were designed to evaluate the long-term nephroprotective effects and safety of sparsentan in patients with IgA nephropathy and FSGS. IgAN and FSGS can progress to end-stage kidney disease. The limited current treatment options in these clinical settings indicate a compelling need to develop an effective and safe nephroprotective therapy. As preliminary results from clinical trials are encouraging sparsentan could become the first drug approved for both IgAN and FSGS.

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LIST OF ABBREVIATIONS:

ANG II – angiotensin II
CHF – congestive heart failure
CKD – chronic kidney disease
DARA – dual action receptor antagonists
ERAs – endothelin receptor antagonists'
ET – endothelin
FPRE – FSGS partial remission of proteinuria endpoint
FSGS – focal segmental glomerulosclerosis
IgAN – immunoglobulin A nephropathy
PAH – pulmonary arterial hypertension
PHN – passive Heymann nephritis
RAAS – renal-angiotensin-aldosteron system
UACR – albumin-to-creatinine ratio
UAER – urinary albumin excretion rate
UP/C – urinary protein-to-creatinine ratio