

ASK1 Inhibitor in Chronic Kidney Disease Therapy: From Bench to Bedside

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KIDNEY360 3: 1128–1131, 2022. doi: <https://doi.org/10.34067/KID.0002562022>

CKD affects a large population of patients worldwide. It is characterized by gradual renal function loss resulting from persistent renal cell death, chronic inflammation, and fibrosis, and currently, effective treatment to reverse disease progression is lacking. In the recent study by Badal *et al.* (1), the authors examined the therapeutic effects of an apoptosis signal regulating kinase 1 (ASK1) inhibitor selonsertib in hypertension-induced glomerulosclerosis and renal function loss, which can be augmented in combination with an angiotensin-converting enzyme inhibitor (ACEi) enalapril. Their results shed new light on the potential clinical application of the ASK1 inhibitor in CKD treatment.

ASK1/MAP3K5, a member of the mitogen-activated protein kinase kinase kinase family, has been identified to play an indispensable role in stress- and cytokine-induced cell death, aberrant cell proliferation, and fibrosis in the last two decades. ASK1 activation mainly occurs during pathologic conditions when a redox responsive protein thioredoxin fails to suppress it after the cellular redox balance is broken. The downstream activated pathways include p38 mitogen-activated protein kinase (MAPK) and c-Jun amino terminal kinase, which are closely related to various diseases in diverse cell types (Figure 1). In tumors, ASK1 activation can lead to apoptosis of cancer cells, amplification of cytokine production in tumor-associated immune cells (primarily macrophages), and degradation of endothelial junction protein VE-cadherin to promote macrophage transmigration (2). In the liver, the inhibition of ASK1 by its inhibitors can attenuate hepatic inflammation and improve nonalcoholic fatty liver disease. It is also reported that ASK1 activation is essential for cardiac hypertrophy, which is verified in an Ang II-induced hypertension murine model by using ASK1 inhibitor selonsertib. In addition, both pharmacological and genetic inhibition of ASK1 in the mouse suppresses the development of bleomycin-induced pulmonary fibrosis (3).

In kidney, ASK1 also shows its tremendous effect on injury and fibrosis regulation. Several *in vitro* studies have indicated the role of ASK1 in oxidative stress-induced apoptosis of different murine kidney cells, including mesangial cells, podocytes, and tubular epithelial cells (4). Moreover, *in vivo* studies have verified

the importance of ASK1 in AKI and repair (5). In both ischemia/reperfusion and unilateral ureter obstruction models, *Ask1*^{-/-} mice showed protective effect on renal injury with reduced activation of p38 MAPK and c-Jun amino terminal kinase compared with wild-type mice. GS-44217, a selective small-molecule inhibitor of ASK1, significantly reduces ischemia/reperfusion and unilateral ureter obstruction-induced AKI in rats. ASK1 is especially noticed to mediate renal injury and fibrosis in CKDs, including diabetic kidney disease (DKD). ASK1 is activated by high glucose and its advanced glycation end products both *in vivo* and *in vitro*, resulting in p38 MAPK signaling pathway activation and renal fibrosis (4). Notably, in renal biopsies from patients with DKD, ASK1 pathway is activated in both glomerular and tubular compartments. Furthermore, GS-44217 can attenuate albuminuria and ameliorate other pathologic features of DKD such as glomerulosclerosis, loss of podocytes, and tubulointerstitial fibrosis in db/db eNOS^{-/-} mice (6).

The universal pathologic role of ASK1 activation inspires enthusiasm to develop ASK1 inhibitors for therapy, and selonsertib has been tested in a few clinical trials (Table 1). It is notable that as a first-in-class, selective, and potent small-molecule inhibitor of ASK1, selonsertib is confirmed to be safe and well tolerated in healthy humans (7). It has been mainly tested for the treatment of fibrotic diseases such as DKD (8), nonalcoholic steatohepatitis (NASH) (9–11), and pulmonary arterial hypertension (12). In the phase 2 clinical trial to evaluate selonsertib's safety and efficacy in adults with treatment refractory moderate-to-advanced DKD, despite the results not meeting the primary efficacy end point (no significant difference of mean eGFR between selonsertib and placebo groups at 48 weeks), *post hoc* analyses showed that selonsertib appears to slow the decline of kidney function after adjusting the confounded eGFR differences at 48 weeks related to the inhibition of creatinine secretion by selonsertib (8). Meanwhile, the phase 2 clinical trial of selonsertib conducted in patients with NASH and stage 2–3 fibrosis shows its promising effect on reducing liver fibrosis (9). Unfortunately, two randomized, double-blind, placebo-controlled, phase 3 trials of selonsertib monotherapy demonstrated no antifibrotic effect in patients with bridging

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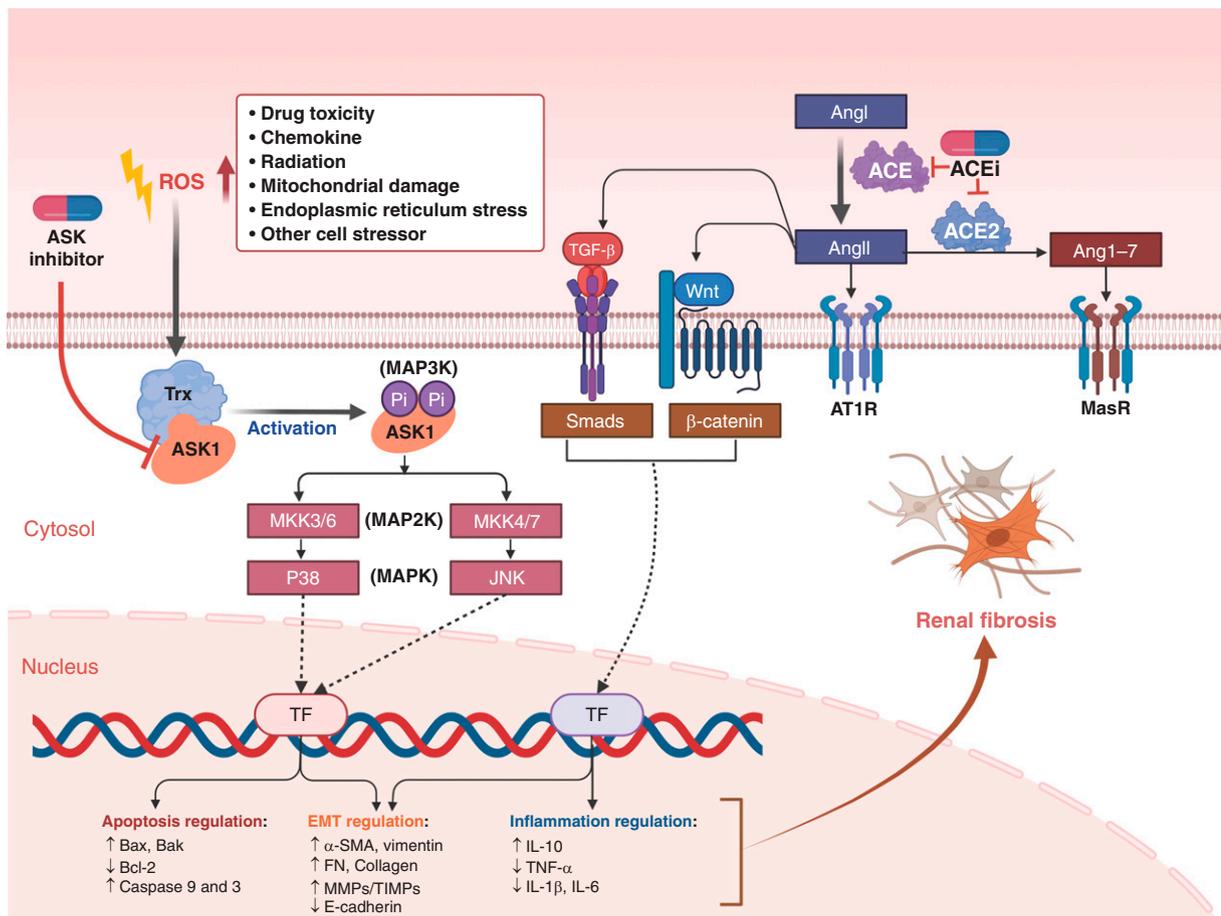


Figure 1. | Apoptosis signal regulating kinase 1 (ASK1) inhibitor and angiotensin-converting enzyme inhibitor (ACEi) mediated protective effect on renal fibrosis. ASK1 inhibitor and ACEi can protect the kidney from fibrosis by blocking different pathways, and their combination has the potential to exert stronger function than monotherapy. When kidney cells are under stress, ASK1 activation will lead to P38 and c-Jun amino terminal kinase pathways activation, and further modulate the transcription of gene expression involved in apoptosis and epithelial/mesenchymal transition (EMT) regulation, which can be suppressed by ASK1 inhibitor. Meanwhile, ACEi may block the activation of TGF- β and WNT/ β -catenin pathways through the modulation of the renin-angiotensin system, which will affect renal fibrosis by suppression of EMT and inflammation. Trx, thioredoxin; Ang, angiotensin; AT1R, angiotensin II type 1 receptor; MasR, Mas receptor; TF, transcription factor; FN, fibronectin.

fibrosis or compensated cirrhosis due to NASH, leading to the termination of both trials (10).

The reason for the failure of these clinical trials remains obscure. One possibility is that injuries in humans are more complicated compared with rodents and may involve redundant pathways other than ASK1 activation. For example, in a study by Sledz *et al.*, selonsertib inhibited murine but not human platelet aggregation (13). Similarly, selonsertib monotherapy suppressed fibrosis in preclinical murine model studies but failed in human clinical trials. In this case, more preclinical research is necessary to identify the potential redundant mechanisms in humans compared with mice, and the combination therapy of ASK1 inhibitor with other drugs may be a new pathway for selonsertib to work for fibrosis treatment.

In this issue of *Kidney360*, Badal *et al.* provide new evidence for the potential combination treatment of ASK1 inhibitor with ACEi enalapril (1). In a hypertensive glomerulosclerosis CKD rat model (5/6 nephrectomy or 5/6 Nx), they evaluated the severity of glomerulosclerosis development in rats with

selonsertib, enalapril, combination (selonsertib+enalapril), and untreated controls. Although selonsertib or enalapril alone can attenuated serum creatinine induction or lower systolic BP and albuminuria, respectively, the combined treatment significantly reduced glomerulosclerosis, renal function decline, podocyte loss, and overall renal apoptosis compared with monotherapy. Their results indicate that selonsertib and ACEi may offer protection from chronic renal injury through different pathways (Figure 1) or work on different renal cells. Selonsertib does not affect the systemic or renal hemodynamics but can inhibit renal cell apoptosis. Meanwhile, enalapril does not suppress cell apoptosis but reduces macrophage infiltration and lowers systolic BP. Overall, it provides prospective evidence for future clinical trials to combine ACEi with selonsertib in CKD patients with hypertensive glomerulosclerosis.

However, there are still some critical concerns to be addressed before moving forward. First, it should be noted that all of these results are still based on rodent models. ACEi may inhibit renal fibrosis by suppression

Table 1. Summary of the clinical trials for selonsertib

Year	Status	Phase	Disease Tested	Trial Objective	ClinicalTrials.gov Identifier	Reference
2015	Completed	1	DKD	To evaluate the pharmacokinetics of selonsertib in participants with normal and impaired hepatic function	NCT02509624	
2014–2016	Completed	2	DKD	To determine the efficacy, safety, and tolerability of selonsertib in participants with DKD	NCT02177786	(8)
2019–2021	Completed	2	DKD	To evaluate the efficacy and safety of selonsertib in participants with moderate to advanced DKD (MOSAIC)	NCT04026165	(8)
2014–2016	Completed	2	PAH	To evaluate the effect of selonsertib in adults with PAH (ARROW)	NCT02234141	(12)
2016–2020	Completed	2	AH	Selonsertib in combination with prednisolone versus prednisolone alone in participants with severe AH	NCT02854631	
2015–2016	Completed	2	NASH	Safety, tolerability, and efficacy of selonsertib alone or in combination with simtuzumab (SIM) in adults with NASH and fibrosis stages F2–F3	NCT02466516	(9)
2016–2018	Completed	2	NASH	Safety, tolerability, and efficacy of selonsertib, firsocostat, and cilofexor in adults with NASH	NCT02781584	(11)
2018–2019	Completed	2	NASH	To evaluate the safety and efficacy of selonsertib, firsocostat, cilofexor, and combinations in participants with bridging fibrosis or compensated cirrhosis due to NASH (ATLAS)	NCT03449446	(11)
2017–2019	Terminated	3	NASH	Safety and efficacy of selonsertib in adults with NASH and bridging (F3) fibrosis (STELLAR-3)	NCT03053050 (STELLAR-3)	(10)
2017–2019	Terminated	3	NASH	Safety and efficacy of selonsertib in adults with compensated cirrhosis due to NASH (STELLAR-4)	NCT03053063 (STELLAR-4)	(10)

DKD, diabetic kidney disease; PAH, pulmonary arterial hypertension; AH, alcoholic hepatitis; NASH, nonalcoholic steatohepatitis.

of different pathways (Figure 1) (14), such as TGF- β pathways or WNT/ β -catenin pathways, which may further regulate various gene expression, including inflammation and epithelial/mesenchymal transition (EMT) related genes. Although the role of complete EMT *in vivo* in renal fibrosis has been questioned, some studies implicate that partial EMT (epithelial cells expressing some mesenchymal markers and with partial phenotype change) may potentially regulate fibroblast activation and fibrosis induction. However, it is unknown whether these pathways are involved in the redundant regulation of renal fibrosis development in humans in addition to ASK1 activation. Second, will further data analysis of previous clinical trial results provide some new information? In the phase 2 DKD clinical trial, the patients also received traditional treatment (ACEis or angiotensin receptor blockers) together with placebo or selonsertib (8). Although ACEis and angiotensin receptor blockers all target the renin-angiotensin-aldosterone system, is there any difference between them when used in combination with selonsertib? In addition, in the phase 3 clinical trial for NASH (10), did any of the patients take ACEi during the treatment, and how was the effect of selonsertib on them compare with others? Third, it is unknown whether the combined effect of ACEi and selonsertib is limited to

hypertension-induced CKD. It is reported that single-nucleotide polymorphisms in the *Ask1* gene are closely related to insulin sensitivity (15). Would this be a reason for the failure of selonsertib monotherapy in DKD patients? Because ACEi has been shown to reduce liver fibrosis (9), can we expect stronger effect from ACEi/selonsertib combination intervention for NASH too?

Although for ASK1 inhibitor the road from bench to bedside seems narrowed after the failed clinical trials, the study by Badal *et al.* (1) suggests that it may find a new way to success in therapy while working together with other drugs. Nevertheless, further clinical trials should depend on more preclinical study to identify the potential redundant pathways in humans and reanalysis of the existing clinical data to identify more evidence for combination use with ACEi.

Disclosures

All authors have nothing to disclose.

Funding

Q. Wei was supported by grant from NIDDK (1 RO1 DK18061-01A1).

Acknowledgments

The content of this article reflects the personal experience and views of the authors and should not be considered medical advice or recommendation. The content does not reflect the views or opinions of the American Society of Nephrology (ASN) or *Kidney360*. Responsibility for the information and views expressed herein lies entirely with the authors.

Author Contributions

Q. Wei reviewed and edited the manuscript, and L. Wen wrote the original draft of the manuscript.

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Received: May 6, 2022 Accepted: May 18, 2022

See related article, “Selonsertib Enhances Kidney Protection Beyond Standard of Care in a Hypertensive, Secondary Glomerulosclerosis CKD Model,” on pages 1169–1182.