

MINI REVIEW

Renin–angiotensin system in intestinal inflammation— Angiotensin inhibitors to treat inflammatory bowel diseases?

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Abstract

Inflammatory bowel diseases (IBDs) are chronic disorders of the gastrointestinal tract, which manifest in recurring gastrointestinal inflammation. The current treatment options of IBD are not curative and are lacking in aspects like prevention of fibrosis. New treatment options are needed to fulfil the unmet needs and provide alternatives to drugs with resistances and side effects. Drugs targeting the renin–angiotensin system (RAS), besides being antihypertensive, also possess anti-inflammatory and antifibrotic properties and could offer an inexpensive alternative to control inflammation and fibrosis in the gut. RAS inhibitors have been effective in preventing and alleviating colitis in preclinical studies, but available human data are still sparse. This review outlines the pathophysiological functions of RAS in the gut and summarizes preclinical studies utilizing pharmacological RAS inhibitors in the treatment of experimental colitis. We discuss the alterations in intestinal RAS and the available evidence of the benefits of RAS inhibitors for IBD patients. Retrospective studies comparing IBD patients using ACE inhibitors or angiotensin II receptor blockers have provided optimistic results regarding a milder disease course and fewer hospitalizations and corticosteroid use in patients using RAS inhibitors. Prospective studies are needed to evaluate the effectiveness of these promising medications in the treatment of IBD.

KEYWORDS

ACE inhibitors, angiotensin II receptor blockers, colitis, inflammatory bowel diseases, renin–angiotensin system

1 | INTRODUCTION

Renin–angiotensin system (RAS) is a network of enzymes and peptides, which regulate blood pressure and fluid homeostasis by stimulating vasoconstriction or relaxation, and aldosterone secretion, and several aspects of

inflammation (Figure 1). Angiotensinogen, which is produced predominantly in the liver, is the precursor peptide for all RAS products, and it is cleaved into angiotensin I (Ang I) by renin. In the classical pathway, angiotensin-converting enzyme (ACE) cleaves Ang I into angiotensin II (Ang II), which is the main effector peptide of RAS.

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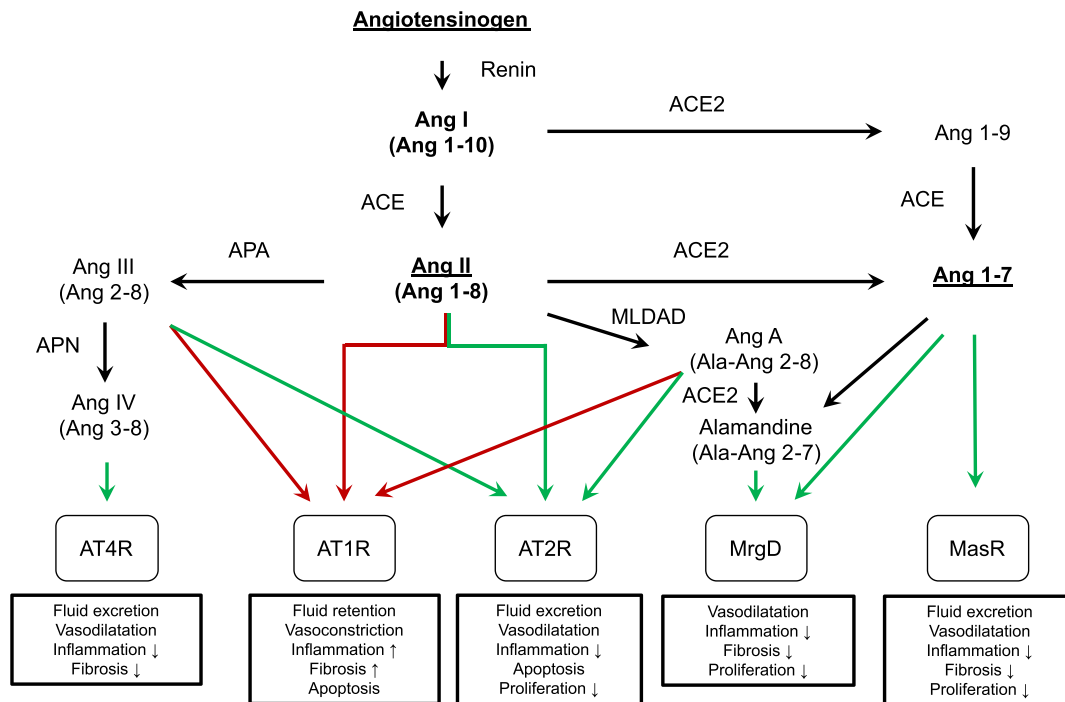


FIGURE 1 The main peptides and enzymes of renin–angiotensin system (RAS). All effector peptides of RAS are derived from the common precursor, angiotensinogen, by the action of several ubiquitously or locally expressed enzymes. Black arrows indicate conversion of peptides, red arrows indicate the activation of the pro-inflammatory AT1R, and green arrows indicate the activation of anti-inflammatory pathways. Ang, angiotensin; ACE, angiotensin-converting enzyme; ACE2, angiotensin-converting enzyme 2; APA, aminopeptidase A; APN, aminopeptidase N; AT1R, angiotensin II receptor type 1; AT2R, angiotensin II receptor type 2; AT4R, angiotensin II receptor type 4; MasR, Mas receptor; MrgD, Mas-related G-protein coupled receptor; MLDAD, mononuclear leukocyte-derived aspartate decarboxylase (modified from previous studies^{3–5})

Ang II acts through the G-protein coupled receptors, angiotensin II receptors type 1 and 2 (AT1R and AT2R), which are present in various tissues and cell types. AT1R is the dominant Ang II receptor, and it promotes increase in blood pressure, inflammation, apoptosis and fibrosis and mediates vasoconstriction, especially in the splanchnic circulation.^{1,2} AT2R is much less expressed in most tissues, and its activation has mostly opposite effects to AT1R. In the alternative RAS pathway, angiotensin-converting enzyme 2 (ACE2) either inactivates Ang II by cleaving one amino acid residue off it, and hence producing Ang 1–7, or directly produces Ang 1–9 from Ang I, thus preventing the formation of Ang II. Ang 1–7 acts through its receptor, Mas receptor (MasR), and largely counters the blood pressure-elevating and pro-inflammatory effects of Ang II. Two more RAS axes have been uncovered (Figure 1). Ang II can be modified by decarboxylation of its first amino acid residue aspartate into alanine, yielding an AT1 and AT2 receptor agonist angiotensin A, which can be cleaved further to form a cardioprotective alamandine acting via Mas-related G-protein coupled receptor D (MrgD).³ Ang II cleavage by aminopeptidase A produces a prohypertensive Ang III,

which can be cleaved by aminopeptidase N into an antihypertensive Ang IV acting through its own AT4 receptor.³ The stepwise cleavage and modification of angiotensin peptides regulate the balance of vasoconstrictive and vasodilatory, and pro-inflammatory and anti-inflammatory, signals, and both the absolute levels and the ratio of Ang II, Ang 1–7 and other angiotensin peptides define the overall outcome in different tissues.^{1–3} Furthermore, there is overlap in affinities of different angiotensin peptides to their receptors, and various enzymes participate in formation of different peptides.⁴

Besides vasculature, RAS acts locally in various tissues including the brain, heart, ocular, reproductive and gastrointestinal tissues.¹ Major sources of renin and angiotensinogen are the kidneys and liver, respectively, but they are also expressed locally. In 2003, ACE2 was identified as the receptor for the severe acute respiratory syndrome coronavirus (SARS-CoV) responsible for an outbreak killing hundreds of people and capable of causing an acute respiratory distress syndrome.⁶ Similarly, ACE2 is the receptor of the SARS-CoV-2, which has caused the presently ongoing coronavirus disease 2019

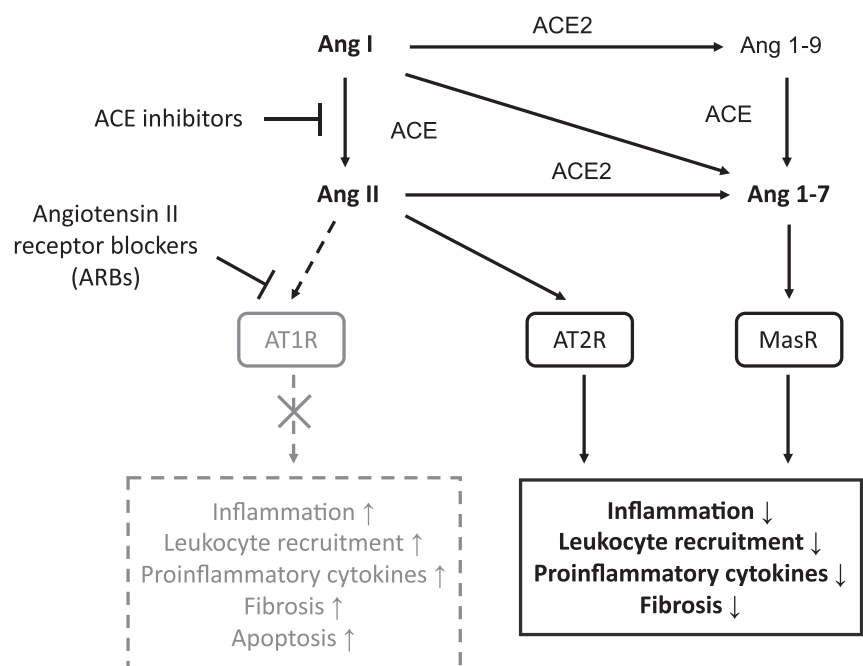
(COVID-19) pandemic.⁷ ACE2 is expressed in respiratory tissues and prominently in the intestine,⁸ probably explaining the possible gastrointestinal symptoms associated with COVID-19.

Inflammatory bowel diseases (IBDs) are chronic diseases that cause recurring inflammation in the gastrointestinal tract. The two forms of IBD are Crohn's disease (CD) and ulcerative colitis (UC). UC affects the mucosa and submucosa of large intestine, whereas CD can affect any part of the gastrointestinal tract, although it most commonly affects the ileum. Unlike in UC, in CD, the inflammation can be transmural, reaching through all layers of intestinal tissue, and leads to development of strictures, fissures and fistulas.⁹ The aetiology is partly genetic, partly environmental and largely unknown, but commonly, a weak host defence against bacterial translocation and inappropriate immune responses leads to chronic inflammation. The inflammatory characteristics of CD and UC share similarities but are also slightly different. In CD, inflammation is generally driven by Th1 and Th17 responses, whereas Th2 type of response is more typical to UC.¹⁰ The recurring flares in IBD are accompanied by extra-intestinal manifestations like uveitis and malnutrition. The treatment strategies in IBD aim to lower inflammation with anti-inflammatory medications, suppress the inappropriate immune responses with immunosuppressants, lower the microbial burden with antibiotics and neutralize inflammatory mediators by biologic therapies, to avoid hospitalizations and surgeries and improve the quality of life of IBD patients. The disease burden of IBD is heavy, as hospitalization and surgical operations are common outcomes in IBD

patients and novel biologic therapies are expensive. The most effective therapies like the anti-inflammatory corticosteroids and immunosuppressive thiopurines also induce side effects, which limit their use, and developing resistance to the biologics is common.¹¹ Chronic inflammation in the intestine can lead to fibrosis and structuring of the damaged intestine, but as of now, there are no generally accepted antifibrotic treatments available for IBD patients.¹²

Pharmacologic inhibition of the classic RAS pathway by ACE inhibitors and angiotensin II receptor blockers (ARBs) is an important treatment strategy against hypertension. ACE inhibitors decrease the production of Ang II, and ARBs antagonize AT1R signalling. These drugs are commonly used, often in combination with other drug classes, and they are well tolerated based on the extensive data that have accumulated of their safety. Besides being antihypertensive, ACE inhibitors and ARBs have anti-inflammatory and antifibrotic properties (Figure 2). Multiple pro-inflammatory signals, like pro-inflammatory cytokines and reactive oxygen species, converge at nuclear factor- κ B (NF- κ B) activation. AT1R signalling leads to NF- κ B activation and production of cytokines in various cell types.¹³ Data from clinical trials point to anti-inflammatory benefits of ACE inhibitors and ARBs in the treatment of many inflammatory conditions, especially in atherosclerosis and in steatohepatitis, nephritis and arthritis.¹⁴ Emerging evidence suggests they could also reduce inflammation in IBD.¹⁵ Here, we review the current knowledge of role of RAS intestinal inflammation and pharmacological RAS inhibition both in animal models of colitis and human IBDs.

FIGURE 2 ACE inhibitors reduce Ang II formation, and angiotensin II receptor blockers reduce activation of AT1R, which reduces pro-inflammatory, profibrotic and proapoptotic signals received by the cell. Additionally, RAS inhibitors might lead to increased binding of Ang II to AT2R or increased production of Ang 1-7 from Ang I or Ang II by various peptidases and elicit direct anti-inflammatory actions via AT2R and MasR. ACE, angiotensin-converting enzyme; ACE2, angiotensin-converting enzyme 2; Ang I, angiotensin I; Ang II, angiotensin II; Ang 1-7, Ang 1-7; Ang 1-9, angiotensin 1-9; AT1R, angiotensin II receptor type 1; AT2R, angiotensin II receptor type 2; ARB, angiotensin II receptor blocker; MasR, Mas receptor



2 | LOCAL INTESTINAL RAS

RAS functions locally in the intestine where it regulates physiological and pathophysiological functions depending on the levels and ratios of the effector peptides. All the main members of classical and alternative RAS, including renin, angiotensinogen, ACE, ACE2, AT1R, AT2R and MasR, have been found in intestines of rodents and humans.^{2,16,17} The other arms of RAS in intestine are largely unelucidated. In normal situations, RAS regulates fluid and electrolyte balance, nutrient absorption and bicarbonate excretion in the intestine. In pathophysiological conditions, RAS is activated in the intestine to produce Ang II, which drives inflammation by inducing the pro-inflammatory NF- κ B, apoptosis and fibrosis via transforming growth factor (TGF)- β 1; induces oxidative stress; and aids in macrophage and neutrophil activation and chemotaxis.^{2,13,18,19}

The function and levels of RAS components in intestine are altered in inflamed intestine. Two of the most used models of IBD in rodents are the dextran sodium sulfate (DSS) and 2,4,6-trinitrobenzene sulfonic acid (TNBS) models, which simulate many aspects of UC and CD. In animal models of colitis, inflammation leads to upregulation of members of both the classical and alternative RAS pathways in intestine. Renin,²⁰ ACE,²¹ AT1R^{20,22,23} and subsequently Ang II^{15,22–24} levels have been shown to be upregulated in both DSS and TNBS colitis models. Members of the alternative RAS pathway, ACE2 and MasR, were increased over the course of DSS colitis in mice, leading to an increase of mucosal but reduction in serum concentration of Ang 1–7.²³

Genetic models that impede Ang II signalling have consistently displayed a milder colitis phenotype than wild type mice.^{18,22,25} Angiotensinogen knockout mice displayed a milder TNBS colitis and lower colonic pro-inflammatory cytokine levels than their wild type counterparts.²⁵ Similarly, a reduced severity of DSS colitis was described in AT1R knockout mice, with milder histological damage of the intestine and lower mucosal markers of inflammation, neutrophil activation and lipid peroxidation compared with wild type mice.²² In another study, the increase of pro-inflammatory tumour necrosis factor- α (TNF- α), monocyte chemoattractant protein-1 (MCP-1) and mucosal addressing cell adhesion molecule-1 (MAdCAM-1) expression was curbed in AT1R knockout mice.¹⁸

RAS activation leads to pro-inflammatory stimulus in the colonic mucosa, which was shown in a study employing renin overexpression and Ang II infusion models.¹⁵ Renin overexpression greatly aggravated TNBS colitis and dramatically increased epithelial apoptosis, and infusion of exogenous Ang II led to a greater

intensity of TNBS colitis evidenced by more extensive histological damage, promotion of epithelial cell apoptosis and elevation of pro-inflammatory cytokine and chemokine levels.¹⁵

ACE ectodomain can be actively cleaved, or shedded, from cell membranes by a disintegrin and metalloprotease 9 (ADAM9) to form an active soluble form of ACE enzyme.^{26,27} The work of our group showed that ACE shedding in intestine is induced by inflammation in DSS colitis.^{28,29} In addition, treatments that aimed to control inflammation, ACE-inhibiting peptide Ile-Pro-Pro and mesenchymal stromal cells, downregulated colonic ACE shedding, implying that cell surface levels of ACE are actively regulated by its shedding.^{29,30} Although RAS is best known as a regulator of blood pressure, it is now clear that RAS participates in various normal and pathophysiological processes in the intestine via its classical and alternative pathways.

3 | RAS IN IBDs

Due to the wide role of RAS in inflammation, fibrosis, immune cell recruitment and apoptosis, imbalance in RAS effectors and activation of classical pathway could play a role in pathogenesis of IBD, but only few studies have explored intestinal RAS in human IBD. The first clues about altered function of RAS in IBD was found already in 1990, when Jaszewski and colleagues reported of elevated levels of Ang I and Ang II in the inflamed colonic mucosa of CD patients.³¹ Ang I and Ang II levels were higher compared with healthy controls or UC patients, and their levels correlated with endoscopic scores of inflammation.³¹ Since then, some studies have reported alterations in mucosal RAS component levels and activities in IBD, but the results have not been completely consistent. In a recent study, *angiotensinogen* gene expression was increased at inflamed sites in colonic biopsies of IBD patients, although no alterations in angiotensinogen or Ang II were seen at peptide level.¹⁷ In another study, *angiotensinogen* correlated with inflammation and disease severity.³² In ileum, however, *angiotensinogen* gene expression was reduced in samples of CD patients.³³ Different studies have reported of increased,²⁰ decreased³² or unchanged¹⁷ *renin* expression in colonic lesions IBD patients. A comprehensive study by Garg and colleagues examined mucosal expression of RAS components at mRNA, protein and activity levels and revealed that ACE2 protein was expressed at higher levels in both inflamed and non-inflamed colons of IBD patients, but its activity was reduced at inflamed sites.¹⁷ The levels of Ang 1–7 and MasR were lower in colons of IBD patients than healthy controls, and AT1R protein

expression was reduced at inflamed sites.¹⁷ Furthermore, fibrosis measured as accumulation of positive Masson's trichrome staining correlated with components of the classical RAS.¹⁷ Another study found a similar increase in *ACE2* gene expression at inflamed sites of colon in both UC and CD patients but a decrease in ileum of CD patients.³² In the same study, mucosal *ACE* was increased in inflamed sites in UC patients, and colonic expression of *ACE2* was increased in CD compared with healthy individuals and correlated with disease scores and serum C-reactive protein in all IBD patients. In addition to intestinal expression of RAS components, the serum activity of ACE and ACE2 activity, and their products Ang II and Ang 1–7, have been compared between IBD patients and healthy controls.³⁴ ACE2 activity and Ang 1–7 levels were elevated in the sera of IBD patients irrespective of their disease status, but no change was found in the classical RAS members.³⁴ As the pro-inflammatory functions of RAS are generally attributed to the classical RAS, the alternative pathway is often uncharacterized but should perhaps be given more attention in future studies.

The inherent differences between UC and CD, invasive sample collection, small study sizes and methodological differences complicate the interpretation of accumulated data. Yet, despite some disparity in findings between the studies, the common trend seems to support the hypothesis that alterations in balance between Ang II and Ang 1–7 levels and their downstream signalling are involved in mucosal inflammation in human IBD as is seen in animal models of colitis.

4 | PRECLINICAL STUDIES OF RAS INHIBITORS IN COLITIS MODELS

The role of RAS in inflammation and the changes in its key enzymes and peptides have sparked interest in the possibility to treat intestinal inflammation with RAS inhibitors (Table 1). The first study to investigate RAS blockade in intestine found captopril to improve TNBS-induced colitis in rats and reduce colonic fibrosis.²⁴ Soon after that, losartan was reported to reduce colitis severity and pro-inflammatory cytokines TNF- α , interferon γ (IFN γ) and interleukin (IL)-1 β in TNBS-treated mice.²⁵ Later, captopril was found to improve aspects of inflammation, oxidative stress and collagen deposition in a rat TNBS model,³⁵ and enalaprilat injections were reported to reduce colonic epithelial cell apoptosis in mouse DSS colitis evidenced as reduced TUNEL positive staining and was associated with increase in anti-apoptotic *Bcl-2* expression.²¹ Since then, various ACE

inhibitors and ARBs have been evaluated in multiple pre-clinical studies employing DSS, TNBS, acetic acid and piroxicam models of colitis in both mice and rats and found to improve different aspects of intestinal inflammation (Table 1). These include the ACE inhibitors enalapril,^{36,37} enalaprilat,^{21,38–40} which is the poorly absorbable active metabolite of enalapril, and captopril,^{24,35} as well as ARBs valsartan,⁴¹ losartan,^{15,25,37,42–44} candesartan,^{18,42} telmisartan^{45–47} and olmesartan.⁴⁸ In addition, renin inhibition with aliskiren reduced TNBS colitis manifestations independently of blood pressure.¹⁵ RAS blockade can antagonize the deleterious effects of colitis by various mechanisms, including curtailing inflammation by reducing pro-inflammatory signals mediated by cytokines and chemokines, suppressing leukocyte recruitment, reducing oxidative stress and controlling fibrosis (Figure 2).

4.1 | Anti-inflammatory effects of RAS inhibitors

A general anti-inflammatory mechanism of RAS blockade is to act on pro-inflammatory leukocytes and inhibit pro-inflammatory cytokine production. Ang II induces pro-inflammatory cytokines in leukocytes, and inhibition reduces it.^{51,52} Ang II induced the production of TNF- α and IL-6, whereas ACE inhibitor captopril treatment reduced LPS-induced TNF- α , IL-1 α , IL-10, IL-12 and IL-18 in dendritic cells.⁵² Captopril, delapril and cilazapril reduced TNF- α production in human peripheral blood mononuclear cells and in vivo in LPS-stimulated mice.⁵¹ Similar effects have been demonstrated in experimental models of colitis. Enalaprilat reduced colonic inflammation measured as IL-1 β and TNF- α expression and histopathological damage in DSS model.³⁸ In our own studies, enalapril reduced the DSS-induced histopathological damage and inflammation by lowering mucosal leukocyte infiltration and *Il-1 β* mRNA expression in colons of mice.³⁷ Luminally administered enalaprilat improved the survival of IL-10 knockout mice following a piroxicam-induced mucosal injury, reduced intestinal permeability and displayed a trend for reducing pro-inflammatory cytokine expression.³⁹ In another study, a losartan analogue CCG-203025 and enalaprilat, which are both poorly absorbed through the intestinal epithelium, were able to reduce the expression of several pro-inflammatory cytokines and chemokines, including IL-1 β , IL-8, IL-6, IFN γ and C-X-C Motif Chemokine 2 (CXCL2) in the piroxicam model in IL-10 knockout mice.⁴⁰ Whether the anti-inflammatory actions of ACE inhibitors and ARBs are mediated mainly via regulation of leukocytes, epithelium or other cell types, or perhaps a combination of all of

TABLE 1 Preclinical trials of RAS inhibitors, activators and genetic models in colitis studies

ACE inhibitors					
Treatment	Dose	Colitis model	Strain	Outcome	Reference
Captopril	50 mg/kg/d	TNBS	Sabra	Reduction of disease activity index, histopathology and fibrosis	Wengrower et al. ²⁴
Captopril or lisinopril	0.1 or 1 mg/kg/d	TNBS	Sprague–Dawley	Reduction of macroscopic and histopathology scores and collagen deposition by captopril	Jahovic et al. ³⁵
Enalaprilat	14.5 µg/d	DSS	C57BL/6	Improved weight, histopathology, reduced apoptosis rate	Spencer et al. ²¹
Enalaprilat	14.5 or 145 µg/d	DSS	C57BL/6	Increased survival, reduced disease activity index, histopathology and fibrosis	Koga et al. ³⁸
Enalaprilat	12.5 mg/kg/d	Piroxicam	IL10 –/– C57BL/6	Increased survival, reduced disease score. Improved histopathology	Sueyoshi et al. ³⁹
Enalapril	1 or 5 mg/kg/d	DSS	C57BL/6	Improvement in histopathology, reduced NF-κB activation and pro-inflammatory cytokines	Lee et al. ³⁶
Enalaprilat	25 mg/kg/d	DSS	IL10 –/– C57BL/6	Improved weight and histopathology, reduced NF-κB activation and pro-inflammatory cytokines	Okawada et al. ⁴⁰
Captopril	5 mg/kg/d	DSS	BALB/c	Unchanged colitis parameters, reduction in colonic <i>angiotensinogen</i> , <i>Ace</i> and <i>Cyp11b1</i> expression	Salmenkari et al. ²⁹
Enalapril	3 mg/kg/d	DSS	BALB/c	Improved histopathology and reduced <i>Il-1β</i> expression	Salmenkari et al. ³⁷
Angiotensin II receptor blockers					
Treatment	Dose	Colitis model	Strain	Outcome	Reference
Valsartan	160 mg/mL	DSS & TNBS	Sprague–Dawley	Improved weight, and histopathology and macroscopic score in TNBS model, reduced diarrhoea in DSS model	Santiago et al. ⁴¹
Candesartan	0.4 mg/kg/d	DSS	C57BL/6	Improved weight, histopathology and TNF-α in AT1R–/–, improved disease activity and body weight by candesartan	Mizushima et al. ¹⁸
Losartan, candesartan, deschloro-losartan	L/DCL 100 mg/kg/d candesartan 10 mg/kg/d	Piroxicam	C57BL/6	Improved histopathology and reduced epithelial cell apoptosis by all treatments	Okawada et al. ⁴²
Losartan	7 mg/kg/d	TNBS	Sabra	Reduced TGF-β-mediated fibrosis by losartan	Wengrower et al. ⁴³
Olmesartan	1, 3 or 10 mg/kg/d	DSS	Wistar	Improved colon length, histopathology and TNF-α	Nagib et al. ⁴⁸
Telmisartan	10 mg/kg/d	TNBS	Wistar	Improved weight, disease activity index and macroscopic and histopathology scores	Arab et al. ⁴⁵
CCG-203025 (losartan analogue)	100 mg/kg	DSS & piroxicam	IL10 –/– C57BL/6	Improved weight and histopathology, reduced pro-inflammatory cytokines in DSS model, improved weight in piroxicam model	Okawada et al. ⁴⁰

(Continues)

TABLE 1 (Continued)

Angiotensin II receptor blockers					
Treatment	Dose	Colitis model	Strain	Outcome	Reference
Losartan	10 mg/kg/d	TNBS	C57BL/6	Improved weight and histopathology and macroscopic scores, reduced apoptosis	Liu et al. ⁴⁴
Losartan	30 µg/kg/d	TNBS	ICR	Milder colitis, impaired IL-1β and IFNγ production	Inokuchi et al. ²⁵
-	-	Ang II infusion + TNBS	C57BL/6	Ang II infusion caused more weight loss, higher histopathology and macroscopic scores, and pro-inflammatory cytokine production.	Shi et al. ¹⁵
Losartan	11 mg/ml (~15 mg/kg/d)	TNBS	C57BL/7	Improved weight, histopathology and macroscopic scores	Shi et al. ¹⁵
Losartan	10 mg/kg/d	DSS	BALB/c	Improved macroscopic and histopathologic inflammation scores	Salmenkari et al. ³⁷
Genetic models					
Animal model	Treatment	Colitis model	Strain	Outcome	Reference
Agt -/-	-	TNBS	Agt -/- ICR	Improved weight and histopathology, impaired IL-1β and IFNγ production	Inokuchi et al. ²⁵
AT1R -/-	-	DSS	AT1R -/- C57BL/6	Improved weight and histopathology, lower TNF-α expression and production	Katada et al. ²²
AT1R -/-	-	DSS	AT1R -/- C57BL/6	Improved weight, histopathology and TNF-α in AT1R -/-, improved disease activity and body weight by candesartan	Mizushima et al. ¹⁸
Renin overexpression	Aliskiren 20 mg/kg/d	TNBS	RenTgMK 129SV	Reduced survival, worse histopathologic and macroscopic scores, increased apoptosis and pro-inflammatory cytokine production in RenTgMK mice. Aliskiren treatment improved all parameters.	Shi et al. ¹⁵
Others					
Treatment	Dose	Colitis model	Strain	Outcome	Reference
Aliskiren	3 or 10 mg/kg/d	DSS	C57BL/6	Improved weight, disease activity index, macroscopy and histopathology at a dose of 10 mg/kg/d	Patel et al. ⁴⁹
Ang 1-7 or A779	0.01-1 mg/kg/d, 1 mg/kg/d	DSS	BALB/c	Ang 1-7 doses of 0.01 and 0.06 mg/kg/day improved weight and histopathology and macroscopic scores and reduced colonic Ang II, A779 worsened histopathological damage	Khajah et al. ²³
Ang 1-7 or A779	0.1 mg/kg/d, 1 mg/kg/d	DSS	BALB/c	Ang 1-7 reduced colonic neutrophil infiltration. Ang 1-7 reduced and Mas antagonist A779 elevated pro-inflammatory cytokines and chemokines	Khajah et al. ⁵⁰

Note: Modified from Salmenkari.⁵

Abbreviations: ACE, angiotensin-converting enzyme; DCL, deschlorolosalartan; DSS, dextran sodium sulfate; L, losartan; RAS, renin-angiotensin system; RenTgMK, renin-overexpressing mice; TNBS, trinitrobenzene sulfonic acid.

them is unclear, but both systemic and luminal administration regimens have shown to be effective.

4.2 | Effect of RAS inhibitors on leukocyte recruitment

RAS inhibitors could potentially reduce leukocyte recruitment by regulating intestinal expression of adhesion molecules. MAdCAM-1 is an adhesion molecule specific to the intestine and gut-associated lymphoid tissue,⁵³ and it binds $\alpha 4\beta 7$ -integrin and L-selectin of T cells to attract lymphocytes to the intestinal lamina propria.⁵³ Lamina propria harbours large amounts of resident leukocytes in physiological conditions in which MAdCAM-1 is expressed at low levels, but inflammation like in IBD increases MAdCAM-1 expression and lymphocyte migration to the inflamed site.⁵³ Ang II increases cellular expression of several adhesion molecules, including VCAM-1, ICAM-1, P-selectin and E-selectin.¹³ AT1R inhibition with candesartan downregulated the TNF- α -induced expression of the intestine-specific adhesion molecule MAdCAM-1, vascular cell adhesion molecule-1 (VCAM-1) and intracellular adhesion molecule-1 (ICAM-1) in endothelial cells and inhibited NF- κ B translocation in vitro.¹⁸ Furthermore, MAdCAM-1 expression and colitis severity were reduced in AT1R knockout mice.¹⁸ Whether RAS inhibition downregulates MAdCAM-1 in wild type animals or humans is yet to be demonstrated, but vedolizumab or natalizumab, which are monoclonal antibodies targeting $\alpha 4\beta 7$ and $\alpha 4$ integrins, respectively, and reduce leukocyte migration to intestine, are both approved for treatment of IBD.⁵⁴ Antibodies targeting MAdCAM-1 have been under development, although phase II studies have not been able to prove their efficacy.^{55,56} RAS inhibition could therefore have potential in controlling leukocyte migration in intestine without the immunogenicity of biologic drugs, but studies directly investigating leukocyte adhesion are needed to address this question.

4.3 | Antifibrotic actions of RAS inhibitors

The anti-fibrotic properties of RAS inhibitors are well established. TGF- $\beta 1$ is a principal growth factor in regulation of tissue healing and collagen deposition, but its excessive activity can lead to fibrosis and decline of organ function.⁵⁷ TGF- $\beta 1$ promotes fibrosis by stimulating collagen synthesis and fibroblast production and by inhibiting extracellular matrix degradation.⁵⁷ Ang II is profibrotic via AT1R-mediated induction of TGF- $\beta 1$

expression, and RAS inhibitors reduce fibrosis in several disease models.⁵⁸ Several preclinical studies have investigated the antifibrotic potential of RAS blockade in chronic colitis models. ACE inhibition by colonic administration of enalaprilat was able to reduce fibrosis in the DSS model by downregulating TGF- $\beta 1$, Smad 3 and 4 and collagen synthesis.³⁸ Both ACE inhibition by captopril and AT1R blockade with losartan were able to reduce colonic fibrosis in a rat model of chronic TNBS colitis, which was accompanied by a reduction in mucosal Ang II and TGF- β levels.^{24,43} Captopril and, to a lesser degree, lisinopril reduced DSS-induced collagen deposition in colons of rats in an acute TNBS model.³⁵ Currently, there are no sufficient antifibrotic therapies available in IBD making ACE inhibitors and ARBs particularly interesting in this regard.

4.4 | Effects of RAS inhibitors on oxidative stress

Ang II induces oxidative stress by activating NAD(P)H oxidase that can be ameliorated by RAS inhibition.⁵⁹ Olmesartan improved markers of oxidative stress by reducing myeloperoxidase (MPO) activity and levels of malondialdehyde (MDA) and increased levels of reduced glutathione (GSH) in a rat DSS model.⁴⁸ Telmisartan is an ARB that, in addition, is a partial agonist to the anti-inflammatory peroxisome proliferator activated receptor-gamma (PPAR- γ), a target of the anti-inflammatory IBD drug 5-aminosalicylic acid.^{60,61} Telmisartan was demonstrated to alleviate TNBS, acetic acid, and DSS colitis models in rats by downregulating pro-inflammatory cytokines, TNF- α and IL-1 β , NF- κ B and its downstream targets cyclo-oxygenase-2 (COX-2) and inducible nitric oxide synthase (iNOS), and their products prostaglandin E₂ (PGE₂) and NO.⁴⁵⁻⁴⁷ Furthermore, telmisartan reduced oxidative stress by normalizing the levels of MDA, nitric oxide, and GSH and activity of superoxide dismutase (SOD) and glutathione peroxidase, and reduced apoptosis by downregulating pro-apoptotic cytochrome c and Bax expression, caspase-3 expression and activity, and upregulating anti-apoptotic Bcl-2.⁴⁵

4.5 | Alternative RAS pathway

The classic RAS pathway is generally considered pro-inflammatory, and the alternative pathway in which ACE2 produces Ang 1-7 to act through MasR is regarded as anti-inflammatory. Indeed, administration of Ang 1-7 alleviated, whereas administration of Mas antagonist A779 aggravated DSS-induced colitis in mice.²³ DSS

colitis was associated with depletion of serum Ang 1–7 and a simultaneous increase in colonic ACE2, Ang 1–7 and MasR levels.²³ Additional work by the same group revealed that several pro-inflammatory cytokines, chemokines and adhesion molecules, including soluble ICAM-1, IL-6 and TNF- α , were reduced by Ang 1–7 treatment, and several pro-inflammatory cytokines, IL-1 β , IL-6 and IL-27, were induced by MasR blockade by A779.⁵⁰ Furthermore, in the same study, exogenous Ang 1–7 treatment was accompanied by reduced neutrophil infiltration to colonic mucosa. Somewhat controversially, ACE2 inhibitor GL1001 improved DSS colitis in BALB/cJ mice by reducing colonic bleeding and diarrhoea, histopathologic damage and MPO activity.⁶² Ang 1–7, produced by ACE2, is generally considered anti-inflammatory and to counter the effects of ACE and Ang II. Byrnes et al. presented the option that other substrates of ACE2, like ghrelin or apelin, could mediate the beneficial effects at least to some degree.⁶²

Clearly, the complexity of the RAS and its interactions with other pro- and anti-inflammatory mediators still requires additional investigation. Data from preclinical studies are encouraging on the potential of RAS inhibitors in intestinal inflammation, and the beneficial mechanisms of RAS inhibitors target several key issues in the pathogenesis of IBD.

5 | RETROSPECTIVE STUDIES IN HUMANS

Despite the known role of ACE inhibitors and ARBs in other inflammatory conditions, there is only little human data on their use regarding IBD, but recently, new retrospective studies have been published with carefully optimistic results. In a study by Shi et al., IBD patients who used ARBs had lower levels of pro-inflammatory cytokines and chemokines in their mucosal biopsy samples than those who were not on ARB therapy.¹⁵ Mucosal levels of the monocyte and macrophage-attracting chemokine, CCL2, the neutrophil-attracting chemokine, CXCL8/IL-8, and pro-inflammatory cytokines IL-1 β , IL-6, IL-23A, TNF- α and IL-17F, were lower on ARB therapy. Clinical outcomes of IBD patients on either ACE inhibitor or ARB therapy have been evaluated recently.^{17,63–65} Jacobs and colleagues found that in a group of IBD patients who were taking ACE inhibitors or ARBs, there were fewer hospitalizations, operations and corticosteroid than in a group who were not on these medications.⁶³ The use of ACE inhibitors or ARBs did not affect new prescriptions of biologics or immunomodulators. The patients were matched according to age, sex, diagnosis and disease location and according to diagnosis

of hypertension, to avoid confounding factor of cardiovascular health status of the patients. In the same study, hospitalizations, operations and corticosteroid use was also compared before and during use of ACE inhibitors and ARBs in a subset of patients who filled both conditions for at least 6 months. RAS inhibitor did not affect these end points in CD patients, but UC patients had less corticosteroid use but more hospitalizations during the period of ACE inhibitor or ARB use.⁶³ Another study compared IBD patients who had been on ACE inhibitor or ARB medication for at least 2 years with those not taking RAS inhibitors and found that RAS inhibitor users had lower disease activity scores and lower faecal calprotectin levels and required fewer hospitalizations.¹⁷ IBD patients who required surgery or hospitalization were less likely to be on RAS inhibitor medications, while other blood pressure lowering medications, statins, antidepressants or NSAIDs, did not have the effect.¹⁷ In another larger set of patients, RAS inhibitor use was associated with higher use of 5-ASA and lower use of biologic drugs, possibly indicating better control of disease, and a trend for fewer flares, resections, glucocorticoid use and hospitalizations, but the effects could not be proven independent of other variables.⁶⁴ Similarly, in one cohort, use of ARBs was associated with lower use of immunomodulators, lower rates of ileocolonic CD location and trends for reduced need of corticosteroids and lower rates of penetrating CD, indicating milder disease, whereas other antihypertensive classes did not associate with altered IBD outcomes.⁶⁵ Previously, IBD patients using β -blockers for hypertension were found to be at increased risk of relapse.⁶⁶ Overall, the few observational studies done to date have provided encouraging results of the benefits of RAS inhibition in IBD, but no prospective studies have been conducted yet.

6 | TIME FOR INTERVENTION TRIALS?

ACE inhibitors and ARBs target several aspects of IBDs, including inflammation, leukocyte recruitment and fibrosis, and could therefore offer a relatively safe and inexpensive option for IBD maintenance therapy.⁶⁷ Currently, there are no antifibrotic therapies available for the treatment of IBD, despite the need.¹² Moreover, if RAS inhibitors would prove to increase the threshold of relapse and slow fibrotic processes in IBD patients, over time, the effects could provide significant improvements to patients and reduce costs in health care. Furthermore, as the mesentery circulation is highly sensitive to Ang II-induced vasoconstriction, RAS inhibition could be beneficial in ischaemic ulcers in Crohn's disease.³³ These

beneficial mechanisms of RAS inhibitors have been elucidated in several preclinical studies using animal models of IBD. However, no prospective clinical trials are registered in ClinicalTrials.gov.

Ang II receptors are found in epithelial, endothelial, mesenchymal and immune cells. Therefore, there is likely no specific target for RAS inhibitors that provide the beneficial effects of RAS inhibition in colitis. It is more likely that the overall intensity and balance of angiotensin receptor signalling is the main contributing effect. As Ang II acts as a pro-inflammatory cytokine, RAS inhibition in IBD could provide a therapy to counter acute inflammation, direct the fate of pro-inflammatory and regulatory inflammatory cells and reduce fibrosis. Prospective studies are needed to confirm the strong theoretical basis and preclinical evidence on the beneficial diverse effects of RAS inhibitors as antifibrotic, anti-inflammatory and antihypoxic medications for IBD.

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CONFLICT OF INTEREST

The authors have no conflicts of interest to declare.

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