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Review Article

Mineralocorticoid Receptor Antagonists for Liver Fibrosis: Potential Mechanisms and Research Progress

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Abstract

Liver fibrosis is a central pathological process driving the progression of chronic liver disease, yet effective antifibrotic therapies remain limited. Increasing evidence has identified the mineralocorticoid receptor (MR), a ligand-activated nuclear receptor, as a key regulator of intrahepatic homeostasis and fibrogenesis. MR is expressed across multiple hepatic cell types, including hepatocytes, hepatic stellate cells, macrophages, and liver sinusoidal endothelial cells, where it integrates metabolic, inflammatory, and microvascular signaling. Under pathological conditions, MR activation—mediated by both aldosterone-dependent and ligand-independent mechanisms such as hypoxia and oxidative stress—amplifies core profibrotic pathways, including TGF-β signaling, reactive oxygen species (ROS) generation, and NF-κB–driven inflammation. These molecular mechanisms are executed in a cell-type–specific manner, promoting hepatic stellate cell activation, macrophage-mediated inflammation, hepatocyte metabolic dysfunction, and liver sinusoidal endothelial cell capillarization, thereby forming a self-reinforcing fibrogenic network. Preclinical studies consistently demonstrate that mineralocorticoid receptor antagonists attenuate fibrosis by targeting these interconnected pathways. However, clinical evidence remains limited, with only early-phase trials in metabolic dysfunction-associated steatohepatitis and indirect support from cardiorenal studies. Nonsteroidal mineralocorticoid receptor antagonists, particularly finerenone, exhibit improved receptor selectivity and safety profiles, highlighting their therapeutic potential. Future research should focus on disease-specific patient stratification, validated antifibrotic endpoints, and rigorous safety evaluation to enable effective clinical translation of MR-targeted therapies in liver fibrosis.

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Introduction

Liver fibrosis represents a common pathological outcome of chronic liver injury and a critical determinant of progression to cirrhosis, portal hypertension, and hepatic failure. Despite advances in etiological therapies, effective antifibrotic strategies that directly target fibrogenesis remain limited.[1]

Recent research has increasingly focused on intrahepatic signaling networks that integrate metabolic dysfunction, inflammation, and microvascular alterations to drive fibrosis progression.[2] Among these, the mineralocorticoid receptor (MR; NR3C2), a ligand-activated nuclear receptor, has emerged as a central regulator of hepatic homeostasis and disease. Notably, MR is expressed across multiple liver cell types, including hepatocytes, hepatic stellate cells (HSCs), macrophages, and liver sinusoidal endothelial cells (LSECs), where it contributes to metabolic regulation, immune responses, and vascular function.[3–5] Under pathological conditions, MR signaling is dysregulated through both ligand-dependent (aldosterone excess) and ligand-independent mechanisms (e.g., hypoxia), leading to activation of profibrotic pathways such as TGF-β signaling, oxidative stress, and immune cell–mediated inflammation. These intrahepatic mechanisms provide a direct biological rationale for targeting MR in liver fibrosis, independent of its established roles in cardiovascular and renal diseases.

Accordingly, this review is structured to first summarize the expression and physiological functions of MR in different hepatic cell types, then discuss the mechanisms by which MR signaling is altered in fibrotic conditions, and finally evaluate preclinical and clinical evidence for mineralocorticoid receptor antagonists (MRAs), with a clear separation of animal and human data and an emphasis on translational relevance.

MR structure and pharmacology

MR is a nuclear receptor with three major functional domains—an N-terminal modulatory domain, a central DNA-binding domain, and a C-terminal ligand-binding domain—enabling ligand-dependent transcriptional regulation after nuclear translocation. In its inactive state, MR resides in the cytoplasm in association with chaperone proteins; ligand binding induces conformational rearrangement, nuclear translocation, and recruitment of transcriptional coregulators that determine gene-specific responses.[6,7]

Although aldosterone is the canonical MR ligand, MR activation in the liver is not strictly ligand-dependent. Pathophysiological conditions such as hypoxia, oxidative stress,

and metabolic injury can promote MR nuclear localization and transcriptional activity, thereby expanding MR signaling beyond classical endocrine regulation. This ligand-independent activation is particularly relevant in chronic liver disease, where local microenvironmental stressors predominate.[5]

Pharmacologically, currently used MRAs are best classified as orthosteric, predominantly competitive antagonists because they bind to the ligand-binding domain and compete with aldosterone or other mineralocorticoid ligands. They are therefore not uncompetitive inhibitors in the enzyme-kinetic sense. Accordingly, a Michaelis constant (Km) is not a meaningful descriptor for MR because MR is a ligand-regulated transcription factor rather than a catalytic enzyme with substrate turnover. Reported Ki/IC_{50} values for MRAs are assay-dependent and reflect ligand binding or functional antagonism rather than enzyme inhibition constants; therefore, they should be interpreted cautiously and contextualized together with receptor conformation and transcriptional effects. However, MR pharmacology cannot be reduced to simple occupancy. Distinct ligands stabilize different MR conformations, which in turn alter nuclear trafficking, DNA binding, and cofactor recruitment. Consequently, steroidal and nonsteroidal MRAs (nsMRAs) produce context-dependent transcriptional modulation rather than uniform receptor blockade.

Classical steroidal MRAs, such as spironolactone and eplerenone, act as competitive antagonists but may display partial agonistic properties under certain conditions, reflecting incomplete suppression of coactivator recruitment. In contrast, nsMRAs (e.g., finerenone) induce alternative receptor conformations that impair coactivator binding and transcriptional activation more effectively. Notably, finerenone has been shown to function as a cofactor-modulating antagonist with inverse agonist activity, suppressing both ligand-induced and basal MR signaling.[8,9]

These structural and pharmacological features position MR as a conformation-sensitive transcriptional regulator, providing a mechanistic basis for the differential efficacy and tissue selectivity of MR antagonists.

Traditional MRAs

The classic MRAs include spironolactone and eplerenone, which are used clinically as diuretics, antihypertensives, and agents for the management of heart failure.[10,11] Spironolactone is structurally similar to aldosterone and competitively binds to MR. The RALES study confirmed that spironolactone significantly reduced mortality in patients with severe heart failure.[10] Eplerenone, a second-generation selective MRA, was similarly shown in the EPHESUS trial to reduce mortality in post-infarction heart failure patients.[11] However, because spironolactone lacks receptor selectivity, it not only blocks MR but also antagonizes androgen and progesterone receptors, leading to endocrine adverse effects such as gynecomastia, menstrual irregularities, and breast tenderness. In addition, both spironolactone and eplerenone carry an increased risk of hyperkalemia, especially in patients with renal impairment, and these issues limit the clinical use of traditional MRAs.[12–14]

nsMRAs (finerenone, apararenone)

To address the limitations of traditional MRAs, a new generation of nsMRAs, including finerenone and apararenone, has emerged. Finerenone is a dihydropyridine-derived compound with notably high affinity and selectivity for MR and virtually no affinity for androgen, progesterone, glucocorticoid, or estrogen receptors.[15] Apararenone (MT-3995) is a nonsteroidal 1,4-benzoxazin-3-one compound that similarly displays high MR selectivity and potent antagonism.[15–17] The two agents differ pharmacokinetically: finerenone is short-acting (elimination half-life approximately 2–3 h) and is administered as the active drug with no active metabolites, whereas apararenone is long-acting with a half-life of approximately 275 h.[18,19] From a safety perspective, finerenone and apararenone have negligible effects on androgen or progesterone receptors and thus rarely induce sex hormone–related adverse events such as gynecomastia or breast discomfort.[14,17] Notably, the high molecular polarity and low lipophilicity of finerenone substantially limit its penetration across the blood–brain barrier. It has a relatively balanced distribution between cardiac and renal tissues, in contrast to steroidal MRAs, which preferentially accumulate within the kidney.[15,20] These pharmacological properties confer only a modest effect on renal tubular sodium–potassium exchange and systemic blood pressure, thereby markedly attenuating the risk of hyperkalemia.[14,20] Taken together, nsMRAs offer significant advantages over conventional steroidal agents, particularly in terms of receptor selectivity, safety profile, and overall tolerability. The structural characteristics and pharmacological properties of representative MRAs are summarized in Table 1.

Clinical evidence

In the cardiorenal field, inhibition of the MR pathway has been firmly established to provide significant clinical benefit. Early landmark trials demonstrated that steroidal MRAs such as spironolactone and eplerenone improved survival and reduced cardiovascular events in patients with heart failure or post–myocardial infarction left ventricular dysfunction.[10,11] Building on this foundation, the novel nsMRA finerenone has shown more consistent and pronounced cardiorenal protection in large-scale randomized controlled trials, leading to its approval for patients with type 2 diabetes and chronic kidney disease.[21–23] Compared with traditional steroidal MRAs, finerenone offers superior efficacy and safety, with lower risks of adverse metabolic and endocrine effects. It has demonstrated benefits across a broad spectrum of cardiovascular and renal conditions—including heart failure, CKD, arrhythmias, and metabolic disorders—highlighting its potential as a next-generation nsMRA with integrated organ protection.[23–27]

Pathological activation of MR in liver fibrosis

Molecular mechanisms linking MR to fibrogenesis

MR activation drives liver fibrosis through a set of interconnected molecular pathways that integrate fibrogenic signaling, oxidative stress, inflammation, and metabolic dysregulation into a self-reinforcing network.

At the core of this process is MR-dependent amplification of TGF-β signaling, which represents the central fibrogenic axis. MR activation upregulates TGF-β1 expression and enhances downstream Smad signaling, thereby promoting HSC activation, myofibroblast transdifferentiation, and excessive extracellular matrix (ECM) deposition.[28–33] In parallel, MR signaling disrupts matrix homeostasis by increasing tissue inhibitor of metalloproteinases-1 (TIMP-1) and suppressing ECM degradation, further favoring fibrosis accumulation.[31,32] A second key mechanism involves oxidative stress mediated by NADPH oxidase-derived ROS. MR activation enhances NADPH oxidase activity, leading to excessive ROS production, which directly induces hepatocellular injury and acts as a potent secondary messenger to amplify TGF-β and NF-κB signaling.[33,34] This establishes a redox-sensitive feed-forward loop that sustains fibrogenesis.[28,29,31,33,35] MR also exerts

Table 1. Structural characteristics and pharmacological properties of representative mineralocorticoid receptor antagonists

Property	Spironolactone	Eplerenone	Finerenone	Apararenone
Chemical structure	Steroidal derivative (pregnane lactone, aldosterone analog)	Steroidal derivative (spironolactone backbone with 9,11-epoxy substitution)	Nonsteroidal small molecule (dihydropyridine scaffold)	Nonsteroidal small molecule (1,4-benzoxazinone scaffold)
MR selectivity	Low – antagonizes MR also androgen and progesterone receptors	Higher – selectively antagonizes MR, with minimal affinity for other steroid receptors	Very high – high affinity for MR with negligible activity at other nuclear receptors	Very high – highly selective MR antagonist
Primary metabolism	Hepatic metabolism to active metabolites (e.g., canrenone)	Hepatic CYP3A4 metabolism; no major active metabolites	Hepatic metabolism; no active metabolites	Hepatic metabolism; likely no active metabolites (limited data)
Elimination half-life	Parent drug ~1.4 h; active metabolites ~16–20 h	~4–6 h	~2–3 h	approximately 275 h (long-acting)
Typical adverse effects	Hyperkalemia; anti-androgenic and anti-progestogenic effects (gynecomastia, sexual dysfunction, menstrual irregularities)	Hyperkalemia; dizziness and mild breast tenderness (low incidence)	Hyperkalemia (manageable); hypotension uncommon; no sex hormone-related adverse effects	Hyperkalemia (mild elevations observed in clinical studies); overall well tolerated

MR, mineralocorticoid receptor; CYP3A4, cytochrome P450 family 3 subfamily A member 4; h, hour(s).

strong proinflammatory effects through activation of NF-κB and inflammasome pathways. MR-dependent transcription promotes the expression of proinflammatory cytokines such as TNF-α and IL-6 and facilitates activation of the NLRP3 inflammasome.[35,36] These processes drive chronic hepatic inflammation and reinforce fibrogenic signaling through immune–stromal crosstalk. Importantly, these molecular pathways do not operate in isolation but are highly interconnected. Oxidative stress enhances TGF-β signaling, inflammation amplifies ROS production, and metabolic dysfunction further drives both inflammatory and fibrogenic pathways. Through this integration, MR functions as a central signaling hub that couples metabolic injury, immune activation, and ECM remodeling into a unified fibrogenic response.[35]

In addition to cell-intrinsic pathways, MR signaling is further modulated by systemic regulatory networks, particularly the renin–angiotensin–aldosterone system (RAAS) and adipokine-mediated metabolic signaling. Activation of RAAS enhances aldosterone availability and amplifies MR-dependent profibrotic signaling, partly through crosstalk with angiotensin II pathways, thereby reinforcing oxidative stress, inflammation, and HSC activation.[30,31,37] Similarly, adipose tissue–derived factors constitute an important metabolic axis linking systemic dysfunction to hepatic fibrosis. Dysregulated adipokine profiles—characterized by increased leptin and reduced adiponectin—promote HSC activation, inflammation, and ECM deposition, whereas MR activation further exacerbates this imbalance.[38–45] Conversely, MR antagonism partially restores adipokine homeostasis and mitigates metabolic stress, thereby indirectly attenuating fibrogenesis. These systemic inputs act as upstream amplifiers of intrahepatic MR signaling, integrating metabolic and hormonal cues into the core fibrogenic network (as shown in Fig. 1).

Cell-type mechanisms linking MR to fibrogenesis

MR signaling contributes to liver fibrogenesis through coordinated effects across multiple hepatic cell types, forming an integrated intrahepatic pathogenic network.

HSCs represent the central effectors of fibrosis.[46,47] MR activation promotes HSC transdifferentiation into myofibroblast-like cells, characterized by increased α-SMA expression, collagen synthesis, and ECM deposition.[28–31,33] This process is mediated primarily through activation of TGF-β/Smad signaling and is further amplified by oxidative stress and inflammatory cues. Pharmacological MR blockade consistently suppresses HSC activation and reduces collagen accumulation across experimental models, establishing HSCs as the primary cellular target of antifibrotic effects.[29,31,32]

Macrophages (Kupffer cells and infiltrating monocytes) function as key amplifiers of MR-driven inflammation. MR activation promotes proinflammatory polarization (M1 phenotype), enhances NF-κB–dependent cytokine production, and facilitates inflammasome activation (e.g., NLRP3), thereby sustaining a profibrotic microenvironment.[36] Macrophage-driven inflammation and immune crosstalk strongly influence fibrogenesis. Myeloid MR deficiency reduces liver steatosis through mechanisms involving adaptive immunity (including $CD8^+$ T-cell activation in non-alcoholic steatohepatitis-like models), suggesting that MR signaling in immune compartments can shape the inflammatory microenvironment that governs HSC activation and fibrosis trajectory.[48]

Hepatocytes play a critical role in linking metabolic stress to fibrogenesis. MR activation in hepatocytes promotes lipotoxicity, oxidative stress, and NF-κB–mediated inflammatory signaling, particularly under conditions of hypoxia or metabolic overload.[5] MR dysregulation disrupts key metabolic regulators, including PPARα and lipid oxidation pathways, thereby contributing to steatosis and secondary activation of nonparenchymal cells.[4] In a cirrhosis model combining CCl_4 exposure and eplerenone treatment, transcriptomic analyses identified downregulation of metabolic process genes in cirrhotic liver tissue that was reversed by eplerenone. Hypoxia in hepatocyte systems partially recapitulated these changes, and eplerenone prevented hypoxia-associated reductions in key metabolic regulators, supporting a hepatocyte-intrinsic MR contribution to metabolic failure and a proinflammatory milieu.[49]

LSECs maintain hepatic microvascular homeostasis through fenestrae-dependent permeability and NO-mediated vasodilation.[50] In chronic liver injury, LSECs undergo capillarization, characterized by defenestration, impaired NO

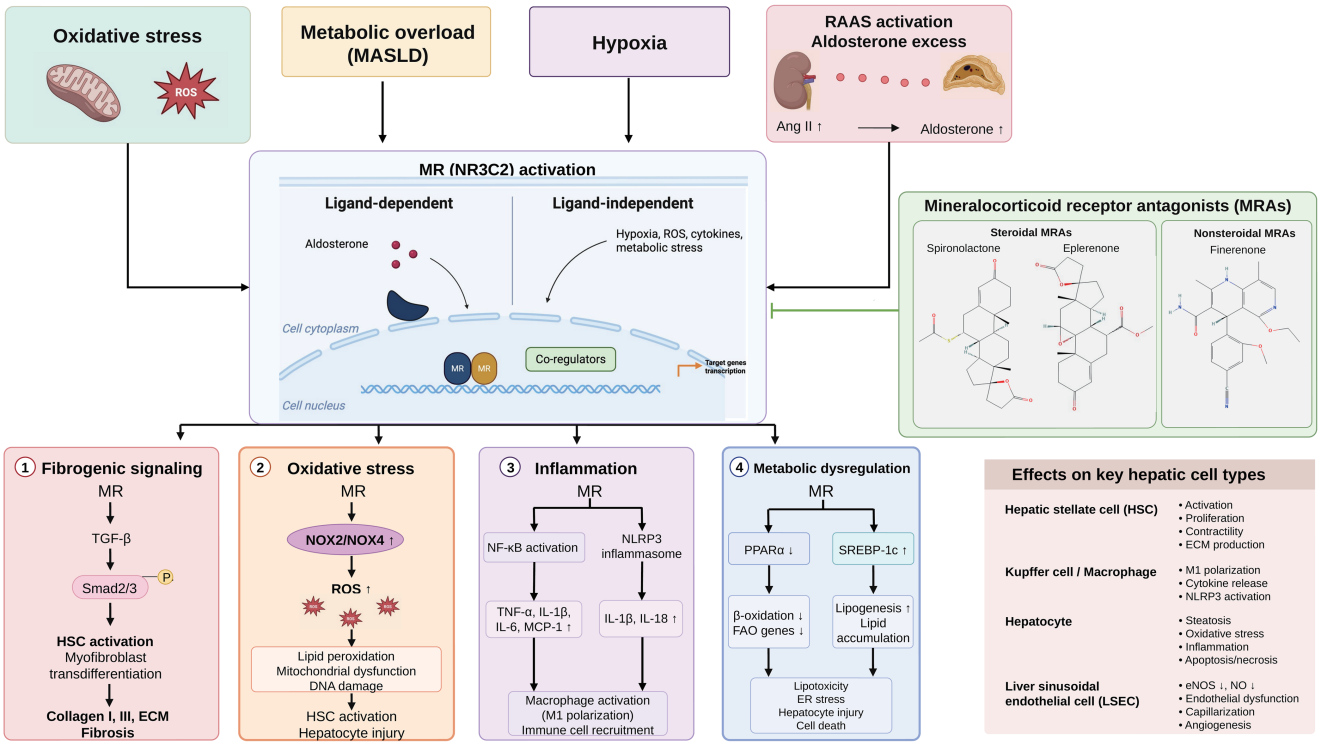

Fig. 1. MR signaling integrates metabolic, inflammatory, and vascular pathways in liver fibrosis and is therapeutically targeted by MRAs. MR overactivation—via RAAS-dependent and microenvironment-driven mechanisms (hypoxia, oxidative stress)—promotes HSC activation, macrophage-mediated inflammation, hepatocyte metabolic dysfunction, and LSEC injury, forming a self-reinforcing fibrogenic network. MRAs disrupt this network by suppressing MR-dependent transcriptional programs, reducing fibrosis, inflammation, and oxidative stress, and restoring intrahepatic homeostasis. Nonsteroidal MRAs exert enhanced effects through cofactor-modulating and inverse agonist properties, supporting MR as a promising antifibrotic target. ↑, increased/upregulated; ↓, decreased/downregulated; Ang II, angiotensin II; ECM, extracellular matrix; eNOS, endothelial nitric oxide synthase; ER, endoplasmic reticulum; FAO, fatty acid oxidation; HSC, hepatic stellate cell; IL, interleukin; LSEC, liver sinusoidal endothelial cell; MASLD, metabolic dysfunction-associated steatotic liver disease; MCP-1, monocyte chemoattractant protein-1; MR, mineralocorticoid receptor; MRA, mineralocorticoid receptor antagonist; NF-κB, nuclear factor kappa B; NLRP3, NOD-like receptor family pyrin domain containing 3; NO, nitric oxide; NOX, NADPH oxidase; NR3C2, nuclear receptor subfamily 3 group C member 2; PPARα, peroxisome proliferator-activated receptor alpha; RAAS, renin–angiotensin–aldosterone system; ROS, reactive oxygen species; SREBP-1c, sterol regulatory element-binding protein-1c; TGF-β, transforming growth factor beta; TNF-α, tumor necrosis factor alpha. Created in https://BioRender.com. Chemical structures were obtained from PubChem.

signaling, and acquisition of proinflammatory phenotypes, thereby initiating HSC activation and fibrogenesis.[50] Mechanistically, MR activation drives LSEC dysfunction by inducing Cav1-dependent oxidative stress, leading to mitochondrial impairment and activation of the AMPK–ULK1 autophagy pathway.[51] This suppresses the eNOS–NO axis, promotes cytoskeletal remodeling, and results in sinusoidal capillarization. MR antagonism reverses these processes, identifying MR-dependent microvascular injury as a key therapeutic target in liver fibrosis.

These cell-type mechanisms converge on a shared set of intracellular effector axes—oxidative stress, inflammatory transcription programs (e.g., NF-κB), metabolic reprogramming, and hemodynamic/microcirculatory dysfunction—providing multiple plausible intervention nodes for MR antagonism (as shown in Fig. 1).

Preclinical and clinical research evidence

Preclinical evidence

Preclinical studies consistently demonstrate that MR blockade attenuates hepatic fibrogenesis through integrated effects on HSC activation, oxidative stress, inflammation, and metabolic regulation. Classical steroidal MRAs provide the most direct experimental support: spironolactone reduces collagen deposition, hepatic hydroxyproline content, and α-SMA–positive HSC activation in toxin- and immune-mediated fibrosis models,[29] while eplerenone inhibits HSC activation, downregulates TIMP-1 to promote matrix degradation, and attenuates oxidative stress and Ang II–mediated signaling.[31]

Mechanistic models further establish aldosterone/MR signaling as a direct driver of fibrosis. Aldosterone combined with high salt induces hepatic fibrosis *in vivo*, characterized by increased TGF-β, α-SMA expression, and oxidative DNA damage, all of which are reversed by MR blockade.[33] *In vitro*, aldosterone directly stimulates HSCs to produce type I collagen and profibrotic mediators, supporting a cell-autonomous MR-dependent pathway.[32]

These effects are most consistent in cholestatic and toxin-induced models (e.g., BDL, CCl_4), where MRAs reduce fibrosis, portal hypertension, and disease progression, partly through suppression of NF-κB signaling and restoration of metabolic regulators such as PPARα and PDK4.[49] In contrast, diet-induced non-alcoholic steatohepatitis models show more variable responses, particularly in inflammatory endpoints. In addition, cell-specific studies highlight the contribution of macrophage MR signaling to metabolic dysfunction and steatosis, as MR deletion improves insulin sensitivity and reduces hepatic lipid accumulation via ERα–HGF–Met signaling.[52]

Overall, while preclinical data strongly support MR blockade as a multifaceted antifibrotic strategy, variability across

models and the predominance of prevention-based designs remain key limitations for clinical translation.

Clinical evidence

In contrast to extensive preclinical data, clinical evidence supporting MRAs as antifibrotic therapies in liver disease remains limited and largely indirect.

The only liver-focused randomized evidence comes from a phase II trial of apararenone in patients with MASH.[53] Although the primary endpoint was not met, apararenone showed trends toward improvement in fibrosis biomarkers, noninvasive scores (ELF, FIB-4), and histological fibrosis stage, suggesting potential antifibrotic activity. However, the small sample size and lack of statistical significance limit definitive conclusions.

Evidence for finerenone is derived mainly from large cardiorenal trials. In the FIDELITY pooled analysis, finerenone did not worsen liver enzymes or fibrosis indices and demonstrated consistent cardiorenal benefits across subgroups with metabolic liver disease.[54] Importantly, safety—including hyperkalemia risk—was comparable to placebo regardless of hepatic status. However, these studies were not designed to assess liver fibrosis outcomes, and surrogate indices such as FIB-4 have limited sensitivity for treatment response.

Overall, current clinical data support the safety and systemic benefits of MRAs in patients with metabolic liver disease but provide insufficient evidence for fibrosis regression.

Practically, MRAs already intersect with hepatology through ascites management. European Association for the Study of the Liver guidance for decompensated cirrhosis describes diuretic strategies, including spironolactone dose ranges, and emphasizes large-volume paracentesis as first-line treatment for grade 3 ascites, framing both the familiarity and the risk context (renal dysfunction and electrolyte disturbances) in cirrhosis care.[55]

Accordingly, future MRA trials in liver fibrosis should: (i) separate antifibrotic endpoints from diuretic/hemodynamic confounding; (ii) predefine clinically relevant outcomes (histologic regression, validated noninvasive fibrosis measures, portal pressure, and decompensation events); and (iii) operationalize safety monitoring consistent with labeling (potassium/eGFR monitoring, hepatic impairment exclusions, and CYP3A4 interaction management).

Advantages and challenges

Advantages

Multiple mechanisms of action: MRAs exhibit anti-inflammatory, antioxidative, and antifibrotic effects, allowing them to simultaneously modulate several key pathways in the development of liver fibrosis. Compared with single-target medicines, this multitarget profile may enhance drug efficacy in inhibiting fibrosis progression.

Systemic protective effects: MRAs have demonstrated significant efficacy in the heart and kidneys. Improvements in cardiac remodeling and renal fibrosis may, via a "heart–kidney–liver" axis, lead to an overall reduction in systemic metabolic inflammation. For example, reducing the fibrosis burden in the heart and kidneys helps lower chronic inflammation levels, which can indirectly slow the progression of liver fibrosis.

Safety and tolerability: nsMRAs, especially finerenone, are more selective than traditional MRAs and cause fewer adverse effects, with a lower incidence of hyperkalemia and virtually no adverse endocrine effects (e.g., gynecomastia).[14] Their effect on blood pressure is minimal, making them safer for use in patients with liver disease, who often have coexisting heart failure or chronic kidney disease. These features provide a favorable clinical application profile.

Challenges

Limited pharmacokinetic data in advanced liver disease: Finerenone is metabolized primarily by the liver. Although dose adjustment is feasible for mild-to-moderate hepatic impairment,[14] there is a lack of robust pharmacokinetic and safety data in patients with advanced cirrhosis. Late-stage fibrosis is often accompanied by portal hypertension and altered drug metabolism, so careful evaluation of finerenone dosing and potential risks in this population is needed.

Insufficient clinical evidence in liver fibrosis: To date, no randomized controlled trials have specifically evaluated finerenone for the treatment of liver fibrosis. The current supporting evidence is largely derived from subgroup analyses of cardiorenal trials and indirect inference. Establishing the efficacy of finerenone in treating liver fibrosis will require more high-quality clinical studies. Furthermore, the antifibrotic efficacy of MR antagonism might differ depending on the underlying liver disease etiology (viral, metabolic, etc.), which also needs to be investigated.

Conclusions

Reversing and treating liver fibrosis remain major challenges in hepatology, and currently, there is a lack of ideal antifibrotic drugs. Based on the pivotal role of the aldosterone–MR pathway in inflammation and fibrosis, MRAs constitute a novel therapeutic approach for antifibrotic treatment. Preclinical data consistently demonstrate that MRAs suppress HSC activation, oxidative stress, and inflammatory remodeling while restoring metabolic balance. New-generation nsMRAs, especially finerenone, combine potent antifibrotic and anti-inflammatory properties with superior receptor selectivity and safety. Although the current evidence is derived mainly from cardiorenal studies and small MASH trials, these findings underscore their translational potential in liver disease. Clinically, translating these findings will require careful patient stratification (e.g., metabolic vs. cholestatic etiologies), selection of appropriate endpoints (including histological improvement, validated noninvasive fibrosis markers, and portal pressure), and integration with existing standards of care. In addition, the use of MRAs in liver disease should include safety monitoring strategies, particularly for hyperkalemia, renal function, and drug–drug interactions, especially in patients with advanced fibrosis or cirrhosis.

In the future, more studies are needed to evaluate the use of nsMRAs in various liver disease settings, including investigations of their pharmacokinetics, efficacy, and safety in advanced fibrosis. Well-designed randomized controlled trials specifically targeting liver fibrosis are essential to define the therapeutic positioning of MRAs, including their potential role in combination regimens with metabolic, anti-inflammatory, or antifibrotic agents. In conclusion, MRAs, particularly finerenone, may become an important component of combination therapy strategies for liver fibrosis, offering a potential therapeutic option for patients with chronic liver disease.

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Author contributions

Study conception, structure design (YF), literature search, data interpretation, and manuscript drafting (HZ). All authors critically revised the manuscript and approved the final version for submission.

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