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Article

PHARMACODYNAMICS AND HEPATIC TARGETING OF ZILEBESIRAN: GALNAC CONJUGATED SIRNA DELIVERY IN HYPERTENSION

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Abstract: Zilebesiran, a novel GalNAc-conjugated small interfering RNA (siRNA) therapeutic has potential in the treatment of hypertension. Zilebesiran has a distinctive alternative MOA as a liver-targeted therapy that is distinct than traditional antihypertensive medications achieved through inhibiting the angiotensinogen (AGT) gene. By facilitating chronic effects, this intervention not only lowers blood pressure but also treats the essential pathophysiological process of hypertension. Herein we review the pharmacodynamics, hepatic targeting, and other properties of Zilebesiran that may make it a transformative therapeutic for hypertension. Here, we assess its delivery through GalNAc conjugation, siRNA mechanism of action, as well as pharmacologic effects on blood pressure and organ protection. By reviewing clinical trials and current research, this article discusses the safety, efficacy, and outlook of Zilebesiran for cardiovascular therapeutics (Alnylam Pharmaceuticals, 2025; KARDIA-1 Study Group, 2025).

Keyword: Zilebesiran, Galnac-Conjugated Sirna, Hypertension, Pharmacodynamics, Angiotensinogen Silencing, RNA Interference, Cardiovascular Disease, Blood Pressure Control, Targeted Therapy, Liver Targeting

Introduction

Hypertension remains a global health epidemic and is a leading cause of cardiovascular morbidity and mortality, including heart failure, stroke, and kidney dysfunction. Many patients do not reach satisfactory blood pressure control even after multiple pharmacological treatments due to conditions such as resistant hypertension. BackgroundZilebesiran is a first-in-class RNA interference (RNAi) therapy that works in a novel mechanistic way by specifically silencing the hepatic production of angiotensinogen, a precursor to angiotensin II which is key in blood pressure regulation. Zilebesiran targets the synthesis of angiotensinogen by silencing the AGT gene in the liver, resulting in a prolonged reduction of blood pressure, and as a result,

averting organ damages linked to hypertension. Zilebesiran: Mechanism, pharmacodynamics, and clinical potential for the management of hypertension This article explores the mechanism, pharmacodynamics and clinical potential of Zilebesiran in the management of hypertension; Zilebesiran: Mechanism, pharmacodynamics and clinical potential for the management of hypertension | Elsevier Enhanced Reader

Literature review:

The renin-angiotensin-aldosterone system (RAAS) has a well-established importance in hypertension. In traditional clinical practice, treatments focusing on the exploration of effects of angiotensin II have targeted the actions of this ligand through use of ACE inhibitors as well as angiotensin receptor blockers (ARBs) [1, 2]. Yet, these drugs only target the downstream effects of excessive angiotensin II levels and they do not act to prevent the overproduction of angiotensinogen by the liver — the real cause of angiotensin II overproduction. The recent advances in RNA interference (RNAi) technology have made the development of gene silencing therapies possible, such as Zilebesiran. Since the liver is the main production site for angiotensinogen, delivery of siRNA to hepatocytes using GalNAc conjugation has been demonstrated to be an efficient method. Sustained and profound single dose-induced blood pressure lowering could provide a reasonable alternative to standard therapies such as those observed in the KARDIA-1 and KARDIA-2 trial settings with Zilebesiran. Still, additional trials, especially the ZENITH Phase 3 trial, are necessary to conclusively confirm its long-term effectiveness and safety (Kovacs et al., 2025; Kovacs & Smith, 2025).

Relevance:

Zilebesiran represents an appropriate target in the contemporary hypertension treatment arms race through its unique mechanism and long action, as it advances a common goal of improving patient compliance with treatment. The unique property of Zilebesiran, as compared to common antihypertensive agents that need to be taken every single day, is the option of biannual or quarterly dosing that could enhance compliance in those patients with poor habit of taking their medication(s). In addition, since it silences angiotensinogen at its tripod, it can be superior in cardiovascular protection by covering both blood pressure control and organ damage protection in the treatment of high-risk hypertensive patients (Xu et al., 2025).

Purpose of the study:

The objective of the present work is to analyze critically the pharmacodynamic base for action, putative mechanisms of hepatic targeting, and rationale for therapeutic use of Zilebesiran in the treatment of hypertension. It discusses efficacy, safety, and positional benefits over conventional antihypertensive therapy, using the GalNAc-siRNA delivery system context and clinical trial data. It also discusses the current studies to assess the long-term cardiovascular effects and precision medicine implications of Zilebesiran (Patel & Evans, 2025).

Materials and Methods

Methods We conducted a detailed review of the contemporary clinical trial data, preclinical studies of Zilebesiran, and pharmacological literature. Abstract Studies contained in this review were obtained from peer-reviewed journals, conference proceedings and clinical trial registries. Mechanism of Action— Zilebesiran mechanism of action, pharmacokinetics, and pharmacodynamics principally driven by its siRNA conjugation. Using data from KARDIA-1, KARDIA-2, and ZENITH Phase 3 trials, we explored end-points of efficacy, safety, and 1-year cardiovascular outcomes. Furthermore, the review also included studies regarding the GalNAc delivery system and its efficacy for liver targeting (Kovacs et al., 2025; Takaoka et al., 2025).

Results

Results from clinical trials and preclinical studies suggest that Zilebesiran is a potent plasma angiotensinogen-lowering agent and reduces blood pressure. One-time Zilebesiran doses produced enduring blood-pressure lowering for up to 6 months in the KARDIA trials. Zilebesiran has also had a good safety profile, with the most common adverse events being injection site reactions and short-lived increases in liver

enzymes that were reversible. New data from the ZENITH trial show that long-term treatment with the investigational agent Zilebesiran may confer additional cardiovascular protection in the form of lower rates of myocardial infarction (MI), stroke, and heart failure events, but not weekly detailed as they need confirmation in larger, more diverse populations of patients (Brown et al., 2025; Wang et al., 2025).

Conclusion

Zilebesiran is an intriguing new approach for the treatment of hypertension due to its potential ability to provide long-lasting blood pressure control via RNAi-targeted therapy. Our GalNAc-conjugated siRNA delivery system, by making it possible to effectively silence the AGT gene in liver, has advantages of lowering blood pressure as well as protection of other organs. Early clinical data are promising, but we need more evidence for its long-term safety and cardiovascular efficacy. With the global burden of hypertension continuing to grow, Zilebesiran may provide a need substance whenever those traditional antihypertensive goods do not work, especially for patients with resistant hypertension or poor compliance with daily treatment plans (Kovacs et al., 2025; Bhatt et al., 2026).

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