https://nephropathol.com DOI: 10.34172/jnp.2024.22542 J Nephropathol. 2024;13(3):e22542

Journal of Nephropathology

Zilebesiran for treating hypertension; the result of recent findings

Atefeh Saljoughian Esfahani[1], Yasaman Vahdani[2], Payam Peymani[3], Soha Razmjouei[4], Mahdieh Ahmadnia[5], Hadi Taghavinejad[6], Jyoti Baharani[7], Maryam Bakhshi[8*]

[1]Islamic Azad University of Najaf Abad, Medical Department Affiliated Hospitals, Isfahan, Iran
[2]Department of Biochemistry and Molecular Medicine, University of Montreal, Montreal, Canada
[3]College of Pharmacy, Rady Faculty of Health Sciences, University of Manitoba, Winnipeg, Manitoba, Canada
[4]Department of Anesthesiology, School of Medicine, Case Western Reserve University, OH, USA
[5]Redland Hospital, Brisbane, Queensland, Australia
[6]Independent Researcher, Anesthetist and Critical Care Specialist, 58/44, Sturegen Street, Ormiston, Brisbane, Queensland 4160, Australia
[7]University Hospitals Birmingham B95SS, Birmingham, United Kingdom
[8]Nickan Research Institute, Isfahan, Iran

ARTICLE INFO

Article type:
News and Views

Article history:
Received: 2 Jan. 2024
Accepted: 30 Jan. 2024
Published online: 4 Apr. 2024

Keywords:
Zilebesiran
Hypertension
Angiotensinogen
Blood pressure

ABSTRACT

Given the pressing need for new medications with minimal adverse effects to address uncontrolled hypertension, this manuscript explores the potential of Zilebesiran as a crucial therapeutic agent. Zilebesiran is an experimental RNA interference drug that shows promise in effectively treating high blood pressure (BP) by decreasing the production of angiotensinogen, a key factor in high BP. It does this by targeting the levels of liver angiotensinogen messenger RNA (mRNA). In a study, a single injection of Zilebesiran demonstrated a noteworthy reduction in BP in individuals with mild-to-moderate hypertension, with sustained effects observed for up to 6 months. Those administered with Zilebesiran were more likely to achieve a 24-hour mean systolic BP of less than 130 mm Hg compared to the control group. The sustained reduction in BP implies that Zilebesiran holds the potential for maintaining consistent BP control, enhancing treatment adherence due to infrequent dosing, and improving outcomes for individuals with hypertension. However, it is important to note that the safety and efficacy of Zilebesiran have yet to be evaluated by regulatory bodies such as the U.S. Food and Drug Administration, the European Medicines Agency, or other health authorities. Ongoing research, exemplified by the KARDIA-2 trial, aims to further assess the efficacy and safety of Zilebesiran as a concomitant therapy for adults with hypertension not adequately controlled by standard treatments.

Implication for health policy/practice/research/medical education:
By inhibiting angiotensinogen, Zilebesiran aims to lower blood pressure (BP) levels in individuals with hypertension. Clinical trials have shown promising results, demonstrating its effectiveness in reducing BP. However, further research and testing are still necessary to fully understand the safety and long-term effects of the treatment.

Please cite this paper as: Saljoughian Esfahani A, Vahdani Y, Peymani P, Razmjouei S, Ahmadnia M, Taghavinejad H, Baharani J, Bakhshi M. Zilebesiran for treating hypertension; the result of recent findings. J Nephropathol. 2024;13(3):e22542. DOI: 10.34172/jnp.2024.22542.

Introduction

Uncontrolled hypertension is a complex condition with a variety of treatment options to prevent further complications. Recent studies are continuously exploring new therapeutic options. Zilebesiran is an RNA interference therapeutic agent that reduces the production of angiotensinogen by targeting hepatic angiotensinogen messenger RNA (mRNA) levels (1-3). Zilebesiran has low rates of adverse reactions, with mild reactions at the injection site being the most common, and no prominent alterations in renal or hepatic function were detected. The potential side effects of Zilebesiran, as reported in the phase 2 KARDIA-1 investigation are low with mild reactions at the injection site being the commonest. There

*Corresponding author: Maryam Bakhshi,
Email: maryambakhshi315@gmail.com

News and Views

were 4 non-critical, associated adverse reactions leading to withdrawal in the Zilebesiran groups, including 2 incidences of orthostatic hypotension, one report of an injection site reaction, and one report of elevated blood pressure (BP). These adverse events were mostly mild or moderate in seriousness (3-12).

The phase two KARDIA-1 investigation shows that a solitary injection of Zilebesiran safely and efficiently dropped systolic blood pressure (SBP) in individuals with mild-to-moderate hypertension for up to 6 months (4). The study showed that individuals taking Zilebesiran were more likely to reach a 24-hour mean SBP of less than 130 mm Hg compared to those who did not receive the treatment. Zilebesiran's ability to sustainably reduce BP in the study indicates its potential to maintain constant BP control and enhance medication through multiple dosing (3).

Zilebesiran-the results of investigations

In a phase 1 study, patients were given a single ascending subcutaneous dose of Zilebesiran (10 mg, 25 mg, 50 mg, 100 mg, 200 mg, 400 mg, or 800 mg) or a placebo. The trial found that individuals getting Zilebesiran had declines in serum angiotensinogen concentration communicating to their respective dose, with no cases of hyperkalemia, hypotension, or deteriorating kidney function necessitating intervention. Meanwhile, 5 individuals had mild injection-site reactions (3). In a phase 2 study, patients were randomized to receive one of four doses of Zilebesiran (150 mg every 6 months, 300 mg every 6 months, 300 mg every 3 months, or 600 mg every 6 months) or a placebo. Moreover, this study showed that individuals taking Zilebesiran had significant reductions in SBP, with the largest reductions observed in the 300 mg and 600 mg groups. Following six months, patients getting Zilebesiran were meaningfully more likely to feel 24-hour mean SBP control. The dosage of Zilebesiran in the phase 2 study ranged from 150 mg to 600 mg, administered subcutaneously every 6 months or every 3 months. The optimal dosage for treating hypertension has not been determined yet, and further research is needed to identify the most effective and safe dosage (12).

Conclusion

The limitations and side effects associated with current hypertension treatments underscore the imperative for novel and enhanced therapeutic alternatives. In this context, the emergence of Zilebesiran presents a promising avenue for addressing the challenges associated with hypertension. In recent clinical trials, Zilebesiran demonstrated its potential by targeting a specific gene implicated in BP regulation, showcasing its effectiveness and favorable tolerability as a treatment for elevated BP. These encouraging findings are particularly significant considering the prevalence of hypertension, a pervasive and potentially severe condition that, if untreated, can contribute to heart disease, stroke, and other serious health complications. The promising outcomes of Zilebesiran in this study warrant further exploration and hold promise for advancing hypertension management.

Authors' contribution

Conceptualization: Atefeh Saljoughian Esfahani, Maryam Bakhshi.
Data curation: Atefeh Saljoughian Esfahani, Maryam Bakhshi.
Investigation: Atefeh Saljoughian Esfahani, Maryam Bakhshi.
Resources: Atefeh Saljoughian Esfahani, Maryam Bakhshi.
Supervision: Maryam Bakhshi.
Validation: Atefeh Saljoughian Esfahani, Maryam Bakhshi.
Visualization: Maryam Bakhshi.
Writing–original draft: Atefeh Saljoughian Esfahani, Maryam Bakhshi.
Writing–review and editing: Yasaman Vahdani, Payam Peymani, Soha Razmjouei, Mahdieh Ahmadnia, Hadi Taghavinejad, Jyoti Baharani.

Conflicts of interest

The authors declare that they have no competing interests.

Ethical issues

Ethical issues (including plagiarism, data fabrication, and double publication) have been completely observed by the authors.

Funding/Support

None.

References

1. Addison ML, Ranasinghe P, Webb DJ. Emerging insights and future prospects for therapeutic application of siRNA targeting angiotensinogen in hypertension. Expert Rev Clin Pharmacol. 2023;16:1025-33. doi: 10.1080/17512433.2023.2277330.
2. van Twist DJL, Kalic H. Zilebesiran for hypertension. N Engl J Med. 2023;389:1438-9. doi: 10.1056/NEJMc2310167.
3. Desai AS, Webb DJ, Taubel J, Casey S, Cheng Y, Robbie GJ, et al. Zilebesiran, an RNA interference therapeutic agent for hypertension. N Engl J Med. 2023;389:228-38. doi: 10.1056/NEJMoa2208391.
4. Alnylam Pharmaceuticals. KARDIA: Zilebesiran Phase 2 Clinical Development Overview. 2021. Available from: https://www.alnylam.com/sites/default/files/pdfs/KARDIA-1-Fact-Sheet.pdf.
5. Johnson V. Single RNAi Therapy Injection Controls Mild-to-Moderate Hypertension for 6 Months. 2023. Available

from: https://www.cgtlive.com/view/single-rnai-therapy-zilebesiran-mild-moderate-hypertension-6-months.
6. Denton KM. Progress towards improving blood pressure control. Nat Rev Nephrol. 2023. doi: 10.1038/s41581-023-00798-7.
7. Bateman RM, Sharpe MD, Jagger JE, Ellis CG, Solé-Violán J, López-Rodríguez M, et al. 36th international symposium on intensive care and emergency medicine: Brussels, Belgium. 15-18 March 2016. Crit Care. 2016;20:94. doi: 10.1186/s13054-016-1208-6.
8. Abasheva D, Fernandez-Fernandez B, Ortiz A. Zilebesiran for hypertension. N Engl J Med. 2023;389:1438. doi: 10.1056/NEJMc2310167.
9. Braunwald E. Inhibition of angiotensinogen in the treatment of hypertension. Eur Heart J. 2023;44(47):4909-10. doi: 10.1093/eurheartj/ehad704.
10. Lifschitz M. Zilebesiran for hypertension. N Engl J Med. 2023;389:1438. doi: 10.1056/NEJMc2310167.
11. Granata S, Stallone G, Zaza G. mRNA as a medicine in nephrology: the future is now. Clin Kidney J. 2023;16:2349-56. doi: 10.1093/ckj/sfad196.
12. Hughes S. Single Injection Reduces Blood Pressure for 6 Months: KARDIA-1. Medscape; 2023. Available from: https://www.medscape.com/viewarticle/998666?form=fpf.