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Journal of Endocrinology and Disorders

Aamir Jalal Al-Mosawi *

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Opinion Article

Hypertension Cure Research progress: The use of Zilebesiran in Hypertension

Aamir Jalal Al-Mosawi *

Advisor doctor and expert trainer The National Training and Development Center and Baghdad Medical City.

***Corresponding Author:** Aamir Al-Mosawi, Advisor doctor and expert trainer The National Center of Training and Development and Baghdad Medical City Iraq.

Received Date: 18 August 2023 | **Accepted Date:** 28 August 2023 | **Published Date:** 14 September 2023

Citation: Aamir Jalal Al-Mosawi, (2023), Hypertension Cure Research progress: The use of Zilebesiran in Hypertension, *J. Endocrinology and Disorders*, 7(6): **DOI:10.31579/2640-1045/153**

Abstract

Chronic hypertension is a lifelong condition, and the patients need lifelong treatment with oral anti-hypertensive medications to say healthy and to prevent the development of serious complications. Demands for changing this situation of lifelong dependence on daily medications have been increasing. The aim of this paper is to highlight the recent breakthrough in hypertension research.

Expert opinion: Zilebesiran, a small interfering RNA targeting angiotensinogen has the main advantage of long duration of action which allows meeting many hypertensions patients' demand of avoiding the inconvenience of talking oral hypertensive medication on daily basis. It is worth mentioning that a more optimal blockade of renin-angiotensin-aldosterone system is not the only advantageous therapeutic approach for the treatment of hypertension. Impairment of endothelium-dependent vasodilation has been increasingly recognized as an important contributor for the development of essential hypertension's-arginine is an amino acid that is considered the biological precursor of nitric oxide which is an important contributor to microvascular vasodilation and to the reduction atherosclerosis. Oral L-arginine has been emerging as a new effective approach of reducing blood through improving endothelial function in hypertensive patients.

Key words: hypertension; zilebesiran; expert opinion

Introduction

As early during the 1980s, the role of angiotensinogen and renin-angiotensin-aldosterone system in the development of hypertension has been emphasized, and angiotensin-converting enzyme inhibitors emerged as the most important clinically useful inhibitors of the renin-angiotensin system that were successful in controlling hypertension [1, 2].

In 2011, Niloofar Nobakht (Figure-1) and her research group suggested that angiotensin-converting-enzyme inhibitors and angiotensin-receptor blockers have limited inhibitory activity of the renin-angiotensin-aldosterone system, and more direct inhibitors may overcome some of these limitations and reduce unwanted effects [3].

Figure-1: Niloofar Nobakht

In 2017, Adam E Mullick and his research group also suggested that the renin-angiotensin-aldosterone system inhibitors are probably not the most favorable inhibitors and may have some safety issues.

They reported an experimental model of malignant hypertension resistant to traditional renin-angiotensin-aldosterone system blockade which included spontaneously hypertensive rats fed an 8% NaCl diet. The study showed that treatment of hypertensive rats with angiotensinogen antisense oligonucleotides which target multiple systemic angiotensinogen sites was associated with significant antihypertensive effect which was not seen with captopril and losartan. Treatment with captopril and losartan during salt deprivation was associated with acute renal injury [4].

In 2019, Estrellita Uijl (Figure-2) from the Netherland and her research group reported an experimental study on spontaneously hypertensive rats. Eight rats were treated with angiotensinogen small interfering RNA (siRNA) targeting liver angiotensinogen (Angiotensinogen siRNA), given subcutaneously in a dose of 10 mg/kg every two weeks. Eight rats were treated with oral valsartan 31 mg/kg daily. Eight rats were treated with oral captopril 100 mg/kg daily. Eight rats were treated with valsartan plus siRNA and eight were treated with captopril plus valsartan.

Figure-2: Estrellita Uijl

After four weeks, mean arterial pressure was reduced the most by valsartan plus siRNA, followed by captopril plus valsartan, captopril, siRNA, and valsartan.

siRNA monotherapy and captopril monotherapy improved cardiac hypertrophy similarly, but less than the combined therapies, which also reduced NT-proBNP (N-terminal pro-B-type natriuretic peptide).

siRNA reduced circulating angiotensinogen by 97.9±1.0%, and by 99.8±0.1% when combined with valsartan.

Even though siRNA significantly reduced renal angiotensin I, only treatment with valsartan plus siRNA reduced circulating and angiotensin renal II.

Renin and plasma K^+ levels were increased by all treatments, but more during treatment with valsartan plus siRNA. All treatments had no effects on aldosterone.

This study suggested that eliminating angiotensin II needs eliminating 99% of the circulating angiotensin and the higher lowering of blood pressure and cardiac hypertrophy is associated with maximal blockade of the renin-angiotensin system which was accomplished by valsartan plus siRNA treatment.

Lowering of angiotensin only was as effective as traditional renin-angiotensin system inhibitors.

Finally, Estrellita Uijl and her research group suggested that RNA interference therapy had stable and sustained efficacy that can persist for several week, and thus it can help improving adherence treatment [5].

In 2020, Huang et al reported the interim results from a first-in-human phase 1 study which showed that Zilebesiran (ALN-AGT01), a small interfering RNA (siRNA) targeting angiotensinogen was associated with a dose-related lowering of blood pressure in hypertensive patients.

The hypotensive effect of a single dose 800 mg of Zilebesiran given subcutaneously was sustained long-term effect occurring in association with a decrease in circulating angiotensinogen by >90% for 6 months. The hypotensive effect was sustained for 24-hour, and the systolic blood pressure was lowered by more than 15 mm Hg at 8 weeks.

Zilebesiran was well tolerated, and only five of the 56 patients experienced mild-to-moderate injection site reactions. Treatment was not associated with serious adverse effects, hypotension, or significant abnormalities of liver or renal functions [6].

In 2023, Akshay S Desai (Figure-3) and his research team reported the first phase of a study which included 107 hypertensive patients. In the first part of the study, patients were randomly assigned in a 2:1 ratio to receive either a single ascending dose of zilebesiran (10, 25, 50, 100, 200, 400, or 800 mg) subcutaneously or placebo for six months.

Figure-3: Akshay S Desai

Zilebesiran is a small interfering RNA (siRNA) targeting angiotensinogen. It inhibits synthesis of angiotensinogen in the liver through reducing hepatic angiotensinogen messenger RNA (mRNA) levels.

In the second part of the study, the patients received 800 mg zilebesiran with low salt diet or with high-salt diet. In the third part of the study, the patients received 800 mg zilebesiran plus irbesartan.

In the first part of the study, zilebesiran treatment was associated with a dose correlated reductions in serum angiotensinogen levels. Single doses of zilebesiran 200 mg or more resulted consistent lowering of systolic blood pressure more than 10 mm Hg and diastolic blood pressure more than 5 mm Hg by the eighth week. The hypotensive effect was sustained at 24 weeks.

The second part of study showed that high-salt diet reduced the hypotensive effect, and the third part of the study showed that irbesartan enhanced the hypotensive effect of zilebesiran.

Five of the 107 patients experienced mild, transient injection-site reactions. Treatment was not associated with hypotension, hyperkalemia, or renal function deterioration [7].

Zilebesiran, a small interfering RNA targeting angiotensinogen has the main advantage of long duration of action which allows meeting many hypertensions patients' demand of avoiding the inconvenience of talking oral hypertensive medication on daily basis.

It is worth mentioning that a more optimal blockade of renin-angiotensin-aldosterone system is not the only advantageous therapeutic approach for the treatment of hypertension.

Impairment of endothelium-dependent vasodilation has been increasingly recognized as an important contributor for the development of essential hypertension's-arginine is an amino acid that is considered the biological precursor of nitric oxide which is an important contributor to microvascular vasodilation and to the reduction atherosclerosis. Oral L-arginine has been emerging as a new effective approach of reducing blood through improving endothelial function in hypertensive patients [8, 9].

Expert opinion: Zilebesiran, a small interfering RNA targeting angiotensinogen has the main advantage of long duration of action which allows meeting many hypertensions patients' demand of avoiding the inconvenience of talking oral hypertensive medication on daily basis.

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Acknowledgment

The author has the copyright of all the sketches in this paper.

Conflict of interest: None.

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DOI:10.31579/2640-1045/153