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Zilebesiran: The First siRNA Drug Therapy for Hypertension

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Abstract:- Blood pressure, which includes ischemic heart disease, stroke, and chronic kidney disease, is the leading preventable cause of death from cardiovascular illnesses on a global scale. Worldwide, arterial hypertension ranks first among cardiovascular diseases (CVDs) and has done so for a long time. One of the first drugs to target hypertension using small interfering RNA (siRNA) technology is zilebesiran. Zilebesiran, an RNA interference therapy drug now in development, binds strongly to the hepatic asialoglycoprotein receptor. A therapeutic target for hypertension, it aims to decrease angiotensinogen production by measuring hepatic angiotensinogen messenger RNA (mRNA) quantities. Zilebesiran is a novel, ground-breaking siRNA therapy for the treatment of hypertension that is now in the second stage of clinical studies. How much of it crosses the placenta and whether it might be utilized to treat preeclampsia should be addressed in future research.

Keywords:- *Zilebesiran, Cardiovascular diseases, Renin-angiotensin-aldosterone system, N-acetylgalactosamine (GalNAc), Angiotensinogen (AGT).*

I. INTRODUCTION

In the past 20 years, there has been an increase in the prevalence of hypertension, affecting an estimated 1.3 billion adults (aged 30-79). In terms of non-communicable diseases, it occurs quite frequently. Worldwide, blood pressure is the primary preventable cause of death from cardiovascular diseases, including ischemic heart disease, stroke, and chronic kidney disease. Although there are many good treatment options for hypertension, over 50% of patients still don't achieve the recommended blood pressure levels. [1] This occurs, in part, because patients do not take their medicine as prescribed and doctors do not start or increase antihypertensive therapy. Blood pressure can vary greatly throughout the day and a lifetime, so even if it appears to be under control based on infrequent office measures, it may be poorly managed.[2]

The RAAS, or renin-angiotensin-aldosterone system, is critical for maintaining a healthy blood pressure level. Zilebesiran, an RNA interference therapy drug now in development, binds strongly to the hepatic asialoglycoprotein receptor. Forming zilebesiran, a small interfering RNA [siRNA] is covalently bonded to an N-acetylgalactosamine [GalNAc] ligand. A therapeutic target for hypertension, it aims to decrease angiotensinogen production by measuring hepatic angiotensinogen messenger RNA (mRNA) quantities. Reducing RAAS through this route could theoretically reduce compensatory angiotensin activation caused by inhibiting ACE or ACE receptors, as no angiotensin peptide starts with angiotensinogen. [3] It is possible to preserve angiotensinogen expression in tissues other than the liver by targeting only hepatocytes with the medication. Side effects in other tissues are avoided by this strategy. There was a near-complete knockdown of hepatic angiotensinogen mRNA expression without affecting renal angiotensinogen mRNA, which is consistent with data from preclinical inquiries of a GalNAc-conjugated angiotensinogen siRNA and early clinical outcomes with GalNAc-conjugated antisense oligonucleotides targeting angiotensinogen, indicating that the approach has liver-specific effects. Once every two or four months, under the skin, GalNAc-siRNAs lower blood pressure consistently and for an extended period. All day long, you will feel its effects. [4]

II. EPIDEMIOLOGY OF HYPERTENSION

Worldwide, arterial hypertension ranks first among cardiovascular diseases (CVDs) and has done so for a long time. After a 0.8% increase from 2015, the region expected to have the greatest prevalence of hypertension in men by 2040 is Southeast Asia. The female hypertension prevalence is projected to be highest in Africa, where it has decreased by 7.1% since 2015. In Southeast Asia, the peak prevalence of hypertension for both sexes is projected to rise from 25.1% in 2015 to 25.3% in 2040. South and Southeast Asia are predicted to witness the greatest growth in male and female cases of hypertension. About 29.4 percent of women and 28.8 percent of men in low-income nations will suffer from hypertension. [5] Additionally, the biggest growth in hypertension prevalence is anticipated to occur in low-income nations. In contrast, women (9.7%), transgender persons (13.6%), and men (16.5%) in high-income nations are thought to have the lowest rates of hypertension. It is anticipated that by 2040, the prevalence of hypertension will be higher in men than in women across the globe.[6]

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III. ZILEBESIRAN MECHANISM OF ACTION

One of the first drugs to target hypertension using small interfering RNA (siRNA) technology is zilebesiran. The molecule zilebesiran is composed of two strands of RNA, one of which is a non-guide strand and the other is a guide strand, which is joined together by the N-acetylgalactosamine (GalNAc) linkage. Due to the surface location of the asialoglycoprotein receptor (ASGPR), which interacts with GalNAc, zilebesiran is selectively taken up by hepatocytes when conjugated with GalNAc. [7] Upon entering the hepatocytes through endocytosis, zilebesiran is recirculated to the cell membrane by ASGPR. As the drug eludes the endosome, it binds to the RNA-induced silencing complex (RISC) in the cytoplasm, which houses a functional core of endonucleases. By identifying the anti-sense strand as a "guide strand," it is possible to keep it and release the "nonguided" strand. By cutting the complementary target mRNA of the guide strand AGT mRNA in this instance the RISC-complex silences the AGT gene. Olpasiran, zerlasiran, lepodisiran, and inklisiran are some of the contemporary lipidology medications that use a similar mechanism of action. [8] Because the loss of negative feedback mediated by Ang II (RAAS escape) occurs with long-term use of standard RAAS inhibitor (ACEi or ARB) drugs, there is a compensatory surge in renin (and Ang I in the case of ACEi usage). Possible prevention of RAAS escape could be achieved by zilebesiran treatment, which nearly completely depletes AGT. [9]

The GalNAc-AGT-siRNA's biochemical and clinical effects are prolonged due to its stability and concentration in hepatic endosomes and RISC recycling. The lack of negative feedback mediated by Ang II leads to an increase in renin as a compensatory mechanism after long-term usage of conventional RAS medicines. [8,9] This phenomenon is called RAS escape. Using siRNA therapy to nearly entirely deplete AGT is one potential strategy to prevent RAS escape. The following acronyms are used in the medical field: ACE, ACEI, AGT, Ang I, Ang II, ARB, ASGPR, AT1R, DRI, GalNAc, messenger RNA, RAS, RNA-induced silencing complex, RNAi, siRNA, sympathetic nervous system, and so on. [7]

IV. ANGIOTENSINOGEN-TARGETING SIRNA IN HYPERTENSION

The FDA granted a license to inclisiran in 2021 for the treatment of hypercholesterolemia, bringing the use of small interfering RNAs (siRNAs) from the lab to the patient's bedside. This method is currently being utilized to treat common chronic diseases, whereas it was previously reserved for rare genetic abnormalities. [10] Zilebesiran is a novel, ground-breaking siRNA therapy for the treatment of hypertension that is now in the second stage of clinical studies. Reduced blood pressure is the result of chemically modified siRNA that has been coupled with N-acetylgalactosamine (GalNAc) and injected subcutaneously. This RNA targets angiotensinogen synthesis in the liver and inhibits the formation of angiotensin I and II (Ang II). [11] The absence of negative feedback mediated by angiotensin II and the subsequent drop in blood pressure cause the usual renin-angiotensin system (RAS) medications, such as angiotensin-converting enzyme (ACE) inhibitors and angiotensin II receptor blockers, to cause an inverse effect: an increase in renin levels. A process known as RAS escape occurs when the elevated levels of renin and the physiologically high amounts of angiotensinogen work together to restore the levels of angiotensin II in ACE inhibitors and Ang II competition at the AT1 receptor in Ang II receptor blockers, respectively. By gradually reducing angiotensinogen levels, siRNA therapy has the potential to successfully inhibit RAS and control blood pressure over the long term, even when renin levels rise to compensate. [12,14]

Along with its numerous other advantages, GalNAc-siRNA treatments may improve adherence since they work for a longer period. They are protected from nuclease degradation once bound to the RISC (RNA-induced silencing complex), which is partly explained by their inherent characteristics. The result is a longer biochemical and clinical effect since target messenger RNAs, like angiotensinogen messenger RNA, can be recycled and degraded multiple times. [13] In addition, recent studies suggest that the long-lasting effects of GalNAc-siRNA are mostly due to their accumulation and stability in acidic intracellular compartments such as hepatic endosomes, which occur months after a single SC injection. Better regulation of blood pressure throughout the day may be possible as a result of the prolonged half-life of siRNA therapies; this should improve cardiovascular outcomes. [15]

Phase I tests using zilebesiran (formerly ALN-AGT01) have just ended, and the results show that the drug has a long-term effect. After a single SC dose of 800 mg, circulating angiotensinogen drops by more than 90% over 6 months, with the greatest drop happening around 3 weeks later. Patients' blood pressure continued to drop even after 8 weeks of taking 800 mg of zilebesiran, with a drop of more than 15 mm Hg in 24-hour ambulatory systolic blood pressure.[11,14] Furthermore, zilebesiran had a low incidence of major adverse events, hypotension, and notable changes in renal or hepatic function, and it was well-tolerated, causing mainly mild to moderate injection site responses. Patients without antihypertensive medication who have mild to moderate hypertension are presently being studied in phase II trials using Zilebesiran. Zilebesiran could provide a clear benefit over current medications by offering a simpler treatment schedule that could include dosing every 6 months, thereby satisfying an unfulfilled demand for effective treatment adherence.[16]

Problems such as insufficient tissue penetration, nuclease inactivation, rapid renal elimination, immune activation, and off-target effects are still present, even though zilebesiran employs novel chemical modifications and GalNAc-conjugated delivery to circumvent these issues. Only through larger-scale population trials will its safety be adequately established, especially in hypertension subpopulations characterized by high-risk factors such as heart failure, diabetes, and chronic renal illness.[17] Fortunately, inclisiran, a GalNAc-conjugated siRNA for

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hypercholesterolemia, has a fantastic safety profile and was recently licensed for usage based on larger clinical trials that included over 4,000 individuals. In addition, zilebesiran's sluggish start of effect (days/weeks) due to RNA interference makes it unsuitable as a first-line treatment for accelerated hypertension or as a solo therapy for people with hypertensive urgency. Additionally, zilebesiran's potential to reduce the risk of cardiovascular events, mortality, and organ damage is not yet known.[18] Future research should also focus on the medication's cost-effectiveness (pharmacoeconomics), its interactions with other long-term medications, the role of genetic diversity and biomarkers on clinical response and safety, and other related concerns. A major potential safety concern in the wider therapeutic utilization of zilebesiran is its long-acting/ongoing, RAS-inhibiting, and blood pressure-lowering actions in conditions of hypovolemia and hypotension.[16]

V. HUMAN STUDIES WITH AGT SIRNA

To inhibit the creation of AGT protein, the experimental GalNAc-siRNA therapy zilebesiran targets human hepatic AGT mRNA. Patients with hypertension participated in a multi-part phase 1 first-in-human trial of zilebesiran. Zilabesiran (10–800 mg) or placebo was administered to patients in a single escalating subcutaneous dose. Minimizations of serum AGT (up to >95% in high-dose levels) were linked to zilebesiran in comparison to placebo, and these reductions were dose-dependent. [19] In addition, by week 8 post-treatment, a single dosage of zilebesiran (≥200 mg) consistently reduced systolic (>10 mm Hg) and diastolic (>5 mm Hg) blood pressure. These zilebesiran-mediated reductions persisted throughout the 24-hour diurnal cycle and continued for 24 weeks. We also tested zilebesiran 800 mg's effects on blood pressure with and without irbesartan and under low-sodium and high-sodium dietary settings. While zilebesiran treatment lowered blood pressure, using irbesartan concurrently had the reverse effect; a high-salt diet mitigated this impact.[20] Hepatic AGT targeting via an RNAi approach may be able to reduce blood pressure in humans, according to the phase 1 findings. Zero side events, including hypotension, hyperkalemia, or worsening renal function requiring medical intervention up to 24 weeks after therapy, were reported in patients who tolerated a single 800 mg dosage of zilebesiran. Similar to previous GalNAc-siRNA platform drugs, zilebesiran exhibited a prolonged pharmacodynamic profile of lowering serum AGT and persistently reducing blood pressure for up to 24 weeks.[20]

VI. SAFETY OF AGT SIRNA

Due to the low dosage frequency of siRNA, improved treatment adherence may be an advantage of AGT siRNA over currently available antihypertensive medications. Furthermore, this method provides consistent and long-lasting RAS blockade, in contrast to the intermittent RAS blockade that is achieved with daily dosed medications.[22] Still, in some hypotensive medical situations, including shock or emergency surgery, acute RAS activation might be necessary to keep tissue perfusion and arterial pressure acceptable. Reversal of AGT siRNA-mediated blood pressure lowering in rodent models can be effected either quickly or gradually by administration of Ang II or norepinephrine, or by high-salt intake or fludrocortisone.[18] This indicates that conventional vasopressors could be a potential intervention for emergency hypotensive episodes. Nevertheless, to determine if the outcomes observed in preclinical trials apply to humans, clinical data are required.[19]

During pregnancy, AGT levels can increase by a factor of two to three. Major changes occur in the cardiovascular system, kidneys, and endocrine glands during pregnancy to ensure that the developing baby gets enough blood. It is not recommended to take RAS blockers while pregnant because the RAS is involved in both the adaption process and fetal growth (for example, in kidney development). This probably holds for AGT siRNA as well. However, how much of it crosses the placenta and whether it might be utilized to treat preeclampsia should be addressed in future research.[20]

The buildup of siRNA in the liver raises concerns regarding potential toxicity to the liver as well as inflammatory and immunologic adverse consequences. Over six months, however, no such side effects were noted with inclisiran, a PCSK9 siRNA that targets the liver. It is now well-established that liver-targeting GalNAc-siRNA conjugates have favorable preclinical safety profiles and large therapeutic windows. This is supported by a substantial body of preclinical research work and is supported by authorized clinical products.[18]

VII. LONGER LASTING BENEFITS

Current hypertension drugs, such as angiotensin receptor blockers (ARBs) and angiotensin-converting enzyme (ACE) inhibitors, aim to prevent the body from absorbing hormones that are already present in the bloodstream.[17] Because they are administered orally, ACE inhibitors and ARBs can sometimes cause serious side effects. Due to zilebesiran's direct injection into the liver, the effects can be more precisely targeted with fewer adverse effects. A longer-lasting pharmaceutical action reduces the likelihood of adverse effects and human error. Patients must take their prescription daily for it to be effective. Regular dosing of the medication is necessary. The drug's effects are more uniformly distributed throughout time with just one injection.[11] Desai explained that when people take drugs once or twice daily, their effects go through a peak and a nadir. Although the long-acting injection of zilebesiran has both positive and negative aspects, Desai said that injecting it twice yearly may result in more consistent blood pressure lowering during the 24-hour cycle. Having the ability to control blood pressure regularly can be useful for both individuals and doctors. The potential effects of salt loading and other methods of manipulating blood pressure are the subject of continuing investigation.[16,18]

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➢ *Indications*

To treat hypertension, zilebesiran sodium is currently being developed. The potential medication is injected under the skin. Utilizing enhanced stabilization chemistry (ESC)-GalNAc-conjugate delivery platform technology, the therapeutic candidate was created as a siRNA that targets angiotensinogen (AGT). The treatment of pre-eclampsia was another area of advancement.[20]

VIII. CONCLUSIONS

An innovative and promising approach to targeting the renin-angiotensin system is the suppression of angiotensinogen in the liver by [a tiny interfering RNA]; this method provides specificity, long-term efficacy, and sustained decrease of blood pressure. The results showed that zilebesiran significantly reduced blood pressure, suggesting that biannual dosing may be an option. Over six months, this innovative medication, which uses RNA interference to reduce hepatic angiotensinogen, demonstrated encouraging results, especially at doses of 300 mg or greater. Hyperkalemia and injection site responses were among the moderate adverse events. Zilebesiran may improve hypertension management by lowering treatment complexity and increasing treatment adherence and effectiveness, according to the results. Additional research is needed to determine the safety and effectiveness over the long term, including when used in conjunction with other treatments, as is being investigated in the current KARDIA-2 trial.

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