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Zilebesiran and Hypertension: A Systematic Review

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ABSTRACT:

Zilebesiran is a new experimental treatment designed to lower blood pressure by targeting a substance in the liver called angiotensinogen, which plays a key role in raising blood pressure. The goal of this treatment is to provide long-lasting blood pressure control with fewer doses than current blood pressure medications.This study aimed to evaluate how well Zilebesiran works in lowering blood pressure in people with hypertension (high blood pressure). Researchers looked at studies from PubMed, Cochrane Library, Ovid, and EBSCO up until July 2024. The studies they included were randomized controlled trials (RCTs) comparing Zilebesiran to a placebo (inactive substance) in people with high blood pressure. They focused on the reduction in 24-hour systolic blood pressure (SBP), changes in plasma angiotensinogen levels, and office SBP after three months.

Keywords: Zilebesiran , angiotensinogen , high blood pressure

Introduction:

Hypertension, commonly known as high blood pressure, is a condition where the blood pressure in the arteries is consistently elevated. This can lead to severe health issues, including heart disease, stroke, kidney damage, and more. Often referred to as the "silent killer," hypertension typically has no obvious symptoms until significant health complications occur.

Prevalence and Impact

- Approximately one in three adults worldwide experience hypertension, making it a major risk factor for cardiovascular disease (CVD) and premature death.
- The incidence of hypertension has been steadily increasing, doubling over the past two decades, with the global number of affected individuals continuing to rise.
- Many individuals with hypertension are unaware of their condition, and even among those who are diagnosed, a large percentage struggle with effectively managing it.

Risk Factors

- Genetics: A family history of hypertension can elevate the risk of developing the condition.
- Age: The likelihood of developing hypertension increases as individuals get older.
- Obesity: Being overweight raises the risk of high blood pressure.
- Lack of physical activity: Inactivity is linked to higher blood pressure levels.
- High salt intake: Diets high in salt can cause the body to retain more fluid, increasing blood pressure.
- Chronic stress: Persistent stress can contribute to higher blood pressure.
- Alcohol and tobacco use: Both substances can elevate blood pressure and damage blood vessels.

Management Hypertension is commonly managed through lifestyle modifications such as diet and exercise, in addition to medication. However, adherence to prescribed treatments remains a challenge, as many individuals do not consistently follow their treatment plans.

The Role of the Renin-Angiotensin-Aldosterone System (RAAS) -The RAAS plays a key role in regulating blood pressure through hormones that control blood volume and vessel constriction. Disruption of this system can contribute to the development of hypertension. As a result, targeting specific components of RAAS, such as angiotensinogen, has become a popular approach in developing new treatments for high blood pressure.

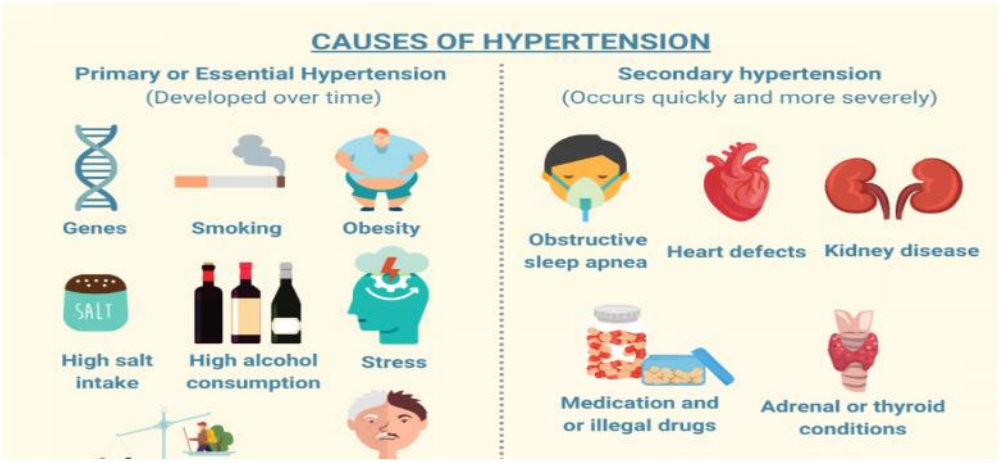

Fig 01 – Causes of hypertension

Zilebesiran is an experimental RNA interference (RNAi) therapy designed to lower blood pressure by targeting the liver's production of angiotensinogen, a key protein in the renin-angiotensin-aldosterone system (RAAS). The RAAS system is crucial in regulating blood pressure, and its overactivation is linked to hypertension. By decreasing the liver's production of angiotensinogen, Zilebesiran seeks to interrupt this pathway, providing a new way to manage high blood pressure.Unlike traditional blood pressure medications that often require frequent doses, Zilebesiran is intended for longer-lasting effects, potentially reducing the need for multiple doses. This could offer a convenient alternative for hypertension patients, especially those who struggle with complex medication regimens. Early clinical trials have indicated that Zilebesiran can significantly lower both systolic blood pressure and plasma angiotensinogen levels, suggesting it could be an effective treatment for primary hypertension.This innovative approach—targeting the liver's production of angiotensinogen—marks a novel strategy in the management of high blood pressure, offering a potentially more convenient and effective treatment for patients.

Mol.Formula- $C_{89}H_{152}N_{16}NaO_{36}P$

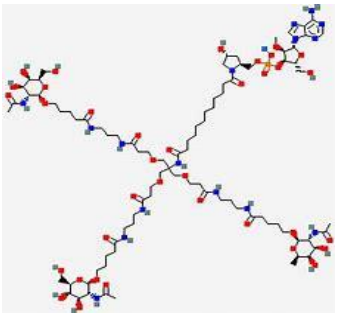

Fig 02 – Structure of Zelebesiran

Mechanism of Action of Zilebesiran

1. Administration of Zilebesiran
   - Zilebesiran is administered via subcutaneous injection.
2. Targeting Liver Cells
   - The drug is conjugated to an N-acetylgalactosamine (GalNAc) ligand.
   - This GalNAc ligand binds strongly to the hepatic asialoglycoprotein receptor (ASGPR) found on liver cells (hepatocytes).
3. Delivery of siRNA to Liver Cells
   - The GalNAc ligand aids in the precise delivery of Zilebesiran (siRNA) to the liver cells.
4. RNA Interference (RNAi) Mechanism
   - The siRNA in Zilebesiran binds to the messenger RNA (mRNA) of angiotensinogen in the liver.
   - This binding prevents the mRNA from being translated into the angiotensinogen protein.
5. Reduction in Angiotensinogen Production
   - The inhibition of angiotensinogen protein synthesis results in lower levels of angiotensinogen in circulation.
   - Reduced angiotensinogen levels help mitigate the activation of the renin-angiotensin-aldosterone system (RAAS), which plays a central role in regulating blood pressure.
6. Lowering Blood Pressure
   - With reduced angiotensinogen levels, the synthesis of angiotensin II, a vasoconstrictor, is diminished.
   - This leads to a decrease in blood pressure.
7. Long-Lasting Effects
   - Zilebesiran has demonstrated the ability to lower blood pressure for up to six months with infrequent dosing, typically administered every 3 to 6 months.

Uses of Zilebesiran

1. Hypertension (High Blood Pressure)
    - Zilebesiran is being developed as a treatment for primary hypertension (essential hypertension), where high blood pressure occurs without an identifiable secondary cause.
    - It works by targeting angiotensinogen, a protein involved in the RAAS pathway, reducing its levels in the liver and thus lowering blood pressure.
2. Long-Lasting Blood Pressure Control
    - One of the key advantages of Zilebesiran is its ability to provide sustained blood pressure control with infrequent dosing (every 3 to 6 months), offering a convenient option for patients who find it difficult to adhere to daily oral medications.
3. Reduction of Angiotensinogen Levels
    - Zilebesiran significantly lowers serum angiotensinogen levels, which is a critical step in regulating blood pressure through the RAAS pathway.
    - Lower angiotensinogen levels result in a reduction in the production of angiotensin II, a potent vasoconstrictor that raises blood pressure.

Clinical Development of Zilebesiran

Zilebesiran is an experimental RNA interference (RNAi) treatment under development for managing hypertension (high blood pressure) by targeting angiotensinogen, a precursor to angiotensin II, which plays a key role in regulating blood pressure. The clinical development of Zilebesiran aims to evaluate its effectiveness, safety, and long-term impact on patients with high blood pressure.

Key Stages of Clinical Development:

1. Phase 1 Clinical Trials
    - Objective: Phase 1 trials were designed to assess the safety, tolerability, pharmacokinetics (how the drug is absorbed and processed in the body), and pharmacodynamics (how the drug affects the body) of Zilebesiran.
    - Findings: The Phase 1 studies indicated that Zilebesiran was generally well-tolerated, with no major safety concerns. The pharmacokinetic data suggested a long half-life, supporting the potential for less frequent dosing.
2. Phase 2 Clinical Trials
    - Objective: A Phase 2 study was conducted to evaluate how effective Zilebesiran is in lowering blood pressure and reducing serum angiotensinogen levels in patients with mild to moderate hypertension.
    - Design: This was a randomized controlled trial where Zilebesiran was administered subcutaneously to hypertensive patients in doses ranging from 50 mg to 500 mg, with dosing intervals of 3 or 6 months.
    - Results: The Phase 2 trial showed that Zilebesiran significantly reduced both 24-hour ambulatory blood pressure and serum angiotensinogen levels in a dose-dependent manner. These effects were sustained for up to six months after a single dose, indicating that less frequent dosing could maintain long-term blood pressure control.
    - Safety: Zilebesiran was generally well-tolerated, with no serious adverse events reported, consistent with the safety profile observed in earlier trials. This supports its potential as a safe and effective treatment option for managing hypertension.

Adverse Drug Reactions (ADRs) of Zilebesiran

Reported Adverse Drug Reactions:

1. Injection Site Reactions:
    - Frequency: Injection site reactions are common with subcutaneous administration of Zilebesiran.
    - Symptoms: These reactions typically include redness, pain, swelling, or irritation at the injection site.
    - Management: These reactions are generally mild and temporary, resolving on their own without medical treatment. They are typical of injectable medications and are not considered major safety concerns.
2. Headache:
    - Frequency: Some patients have reported mild headaches during clinical trials, but these were generally short-lived.
    - Management: Headaches were typically not severe, and most patients recovered without needing to stop treatment.
3. Fatigue:
    - A few trial participants reported mild fatigue, which was usually temporary and subsided over time.
4. Nausea:
    - Frequency: Mild nausea was noted in a small number of patients, but it was neither common nor severe.
    - Management: Similar to other mild gastrointestinal symptoms, nausea was generally brief and resolved without intervention.
5. Elevated Liver Enzymes (Transient):
    - Some patients experienced slight and temporary increases in liver enzymes (e.g., ALT, AST). However, these increases did not result in significant liver damage or require discontinuation of the drug.
    - Management: Regular monitoring of liver function during treatment may be recommended.
6. No Severe Adverse Events:
    - During Phase 1 and Phase 2 trials, no severe adverse events (SAEs) were directly attributed to Zilebesiran.
    - Serious side effects, such as cardiovascular issues or severe allergic reactions, were not observed in the patient populations studied.

Comparison of Zilebesiran with Other Hypertension Therapies

1. **Zilebesiran vs. ACE Inhibitors (Angiotensin-Converting Enzyme Inhibitors)**
    - Mechanism of Action:

- Zilebesiran reduces blood pressure by targeting and decreasing angiotensinogen levels in the liver, which is a precursor to angiotensin II, a protein involved in raising blood pressure.
- ACE inhibitors (e.g., lisinopril, enalapril) block the enzyme that converts angiotensin I into angiotensin II, thus lowering blood pressure by reducing vasoconstriction and aldosterone release.

- Dosing Frequency:
  - Zilebesiran provides long-lasting effects with dosing intervals of 3 to 6 months, offering greater convenience for patients.
  - ACE inhibitors typically require daily administration.
- Efficacy:
  - Both treatments effectively lower blood pressure. Zilebesiran's prolonged effects may offer more sustained control with fewer doses. ACE inhibitors lower blood pressure more immediately but necessitate daily use for continuous results.
- Safety/Tolerability:
  - ACE inhibitors can cause side effects such as a persistent cough, hyperkalemia, and angioedema.
  - Zilebesiran has a favorable safety profile, with mild injection site reactions and occasional transient elevations in liver enzymes. However, long-term safety is still being studied.

2. Zilebesiran vs. Angiotensin Receptor Blockers (ARBs)

- Mechanism of Action:
  - Zilebesiran directly targets angiotensinogen in the liver, reducing the production of angiotensin II.
  - ARBs (e.g., losartan, valsartan) block the receptor for angiotensin II, preventing its vasoconstricting effects and aldosterone release.
- Dosing Frequency:
  - Zilebesiran offers long-term control, with dosing intervals as infrequent as 3-6 months.
  - ARBs generally require daily dosing.
- Efficacy:
  - Both Zilebesiran and ARBs are effective in lowering blood pressure. However, Zilebesiran's innovative mechanism may offer more durable effects with fewer doses, while ARBs provide quicker and more consistent blood pressure management.
- Safety/Tolerability:
  - ARBs are generally well-tolerated, with fewer side effects compared to ACE inhibitors, though dizziness, hyperkalemia, and fatigue may occur.
  - Zilebesiran's side effects are typically mild (e.g., injection site reactions), and its long-term safety profile is still being evaluated

3. Zilebesiran vs. Diuretics

- Mechanism of Action:
  - Zilebesiran lowers blood pressure by targeting angiotensinogen and decreasing angiotensin II levels in the liver.
  - Diuretics (e.g., hydrochlorothiazide, furosemide) work by promoting fluid excretion through the kidneys, which reduces blood volume and, consequently, blood pressure.
- Dosing Frequency:
  - Zilebesiran offers long-term blood pressure management with infrequent dosing every 3 to 6 months.
  - Diuretics typically require daily use.
- Efficacy:
  - Diuretics are particularly effective in patients with fluid retention or in older populations. Although diuretics do not directly target the RAAS system as Zilebesiran does, they remain a cornerstone of hypertension therapy, often used in combination with other drugs.
  - Zilebesiran has demonstrated long-lasting blood pressure reduction, which may improve adherence, especially in patients who struggle with daily medications.
- Safety/Tolerability:
  - Diuretics may cause dehydration, electrolyte imbalances, and kidney issues, which require regular monitoring.
  - Zilebesiran generally has a favorable safety profile, with mild injection site reactions and transient liver enzyme elevations, though liver function monitoring is recommended.

4. Zilebesiran vs. Beta-Blockers

- Mechanism of Action:
  - Zilebesiran lowers blood pressure by reducing angiotensinogen levels and subsequently angiotensin II production.
  - Beta-blockers (e.g., metoprolol, atenolol) lower blood pressure by blocking beta-adrenergic receptors, reducing heart rate and cardiac output.
- Dosing Frequency:
  - Zilebesiran provides long-term blood pressure control with dosing intervals of 3-6 months.
  - Beta-blockers require daily administration, and adherence can be challenging for some patients.
- Efficacy:
  - Beta-blockers are effective in managing blood pressure, especially in cases with tachycardia or arrhythmias. However, they may not be as effective in elderly patients or those with isolated systolic hypertension.
  - Zilebesiran's approach may offer more durable and long-lasting effects, with fewer doses required for blood pressure control.
- Safety/Tolerability:
  - Beta-blockers are generally well-tolerated but can cause fatigue, dizziness, and bradycardia.
  - Zilebesiran's safety profile is favorable, with mild side effects like injection site reactions.

Iron Chelation Therapy for Hypertension

Iron chelation therapy is primarily used to treat iron overload conditions such as thalassemia, hemochromatosis, and transfusion-dependent anemia, where excessive iron builds up in the body. This therapy involves the use of chelating agents that bind to excess iron, facilitating its removal from the body through urine or feces. Recently, there has been growing interest in exploring the potential impact of iron chelation on hypertension (high blood pressure), particularly in patients with conditions where iron overload may contribute to cardiovascular disease or high blood pressure.

Iron Overload and Hypertension

1. Iron's Role in Hypertension:
    - Emerging research suggests that iron overload may play a role in the development of hypertension.
    - Iron is an essential mineral in many biological processes, such as hemoglobin formation and the regulation of vascular tone. However, excess iron can promote the production of free radicals, leading to oxidative stress. This stress can damage blood vessels and increase blood pressure.
    - Iron overload can also lead to vascular damage, inflammation, and altered endothelial function, all of which are mechanisms contributing to increased blood pressure.
2. Potential Mechanisms by Which Iron Chelation Affects Hypertension:
    - Oxidative Stress Reduction: Chelating agents bind excess iron, reducing the formation of free radicals and oxidative stress, which could help lower blood pressure.
    - Vascular Function: Iron chelation may enhance endothelial cell function, reducing iron-induced damage, potentially reducing vascular stiffness and lowering blood pressure.
    - Inflammatory Modulation: Iron overload is associated with inflammation, which can worsen hypertension. By lowering iron levels, chelation therapy may help reduce inflammation and improve vascular health.

Evidence for Iron Chelation Therapy in Hypertension

While iron chelation is not a mainstream treatment for hypertension, several studies have explored its potential benefits, particularly for patients with specific conditions such as hemochromatosis, thalassemia, or those undergoing frequent blood transfusions.

1. Studies in Iron Overload Conditions:
    - Iron overload has been linked to cardiovascular complications, including hypertension. Individuals with conditions like thalassemia or hemochromatosis are at a higher risk of cardiovascular diseases, including hypertension, due to excess iron.
    - A study by Cassar et al. (2014) found that iron chelation therapy in patients with thalassemia was associated with improvements in vascular health and reductions in blood pressure.
2. Animal Studies:
    - Animal models of iron overload suggest that iron chelation can prevent hypertension by reducing oxidative stress and improving vascular function.
    - In a study involving rats, iron chelation with deferoxamine in iron-overloaded rats led to significant reductions in blood pressure and improved vascular compliance, indicating a potential link between iron overload and hypertension (Liu et al., 2011).
3. Human Studies:
    - In clinical settings, iron chelation therapy in patients with iron overload conditions has shown mixed results. Some studies report modest benefits in blood pressure reduction, while others did not demonstrate a direct impact.
    - A study by Buss et al. (2013) found that in patients with hemochromatosis, iron chelation therapy was linked to improvements in cardiovascular function and blood pressure control, particularly in individuals with moderate iron overload.

Iron Chelating Agents Used in Hypertension

1. Deferoxamine:
    - Deferoxamine is a well-known iron chelator that binds free iron and helps eliminate it from the body. It has been primarily used in patients with thalassemia and hemochromatosis.
    - Research indicates that deferoxamine may have beneficial effects on blood pressure in iron-overloaded patients by reducing oxidative stress and improving vascular health.
2. Deferasirox:
    - Deferasirox is an oral iron chelator that is effective at reducing iron overload in patients. There is some evidence suggesting it may help improve cardiovascular health and lower blood pressure in patients with conditions like beta-thalassemia.
    - A study by Girotto et al. (2016) found that deferasirox was associated with reduced iron levels and a decrease in systolic blood pressure in thalassemia patients.
3. Deferiprone:
    - Deferiprone, another iron chelator, is often used in patients with thalassemia to address iron overload. Although less frequently studied for its effects on hypertension, its potential to reduce iron-induced damage could contribute to lowering blood pressure in these patients.

Current Regulatory Status of Zilebesiran

1. Clinical Trials and Ongoing Development:
    - Zilebesiran is currently undergoing clinical trials to assess its effectiveness and safety in treating hypertension. It has progressed to Phase 2 clinical studies, which are evaluating various dosing schedules, including subcutaneous administration every three or six months.
    - These trials are being conducted in multiple countries, with ongoing monitoring of outcomes such as 24-hour systolic blood pressure and plasma angiotensinogen levels.
2. Regulatory Authorities and Approvals:
    - As of now, Zilebesiran has not been approved by major regulatory agencies such as the U.S. Food and Drug Administration (FDA) or the European Medicines Agency (EMA).
    - Both the FDA and EMA are closely tracking its progress through the various phases of preclinical and clinical trials, though it remains unapproved in both the U.S. and Europe.
    - Zilebesiran has been granted fast-track designation due to its potential to address hypertension in specific patient populations, which could help accelerate the review process once sufficient data from ongoing trials are available.
3. Orphan Drug Status:

- For certain indications, such as genetic forms of hypertension (e.g., those linked to mutations in the RAAS pathway), Zilebesiran could potentially qualify for orphan drug status. This designation provides benefits such as tax incentives and market exclusivity for treatments targeting rare diseases. However, as of now, this designation has not been officially granted for Zilebesiran.

4. Pending Regulatory Filings:
   - Zilebesiran is expected to submit regulatory filings to agencies like the FDA and EMA based on the results of ongoing Phase 2 trials. If Phase 3 trials are successfully completed and the drug meets the required efficacy and safety standards, Zilebesiran could receive regulatory approval for treating hypertension.

Conclusion:

Zilebesiran presents a promising new approach for managing hypertension through RNA interference, targeting angiotensinogen to lower blood pressure. Clinical trial results indicate that zilebesiran is effective in reducing 24-hour systolic blood pressure and office blood pressure, with effects lasting several months following a single dose. Its extended duration of action allows for dosing intervals of 3 to 6 months, which could enhance patient adherence compared to daily medications. While the drug's safety profile appears favorable, additional research is necessary to confirm its long-term efficacy and safety before it can receive regulatory approval. If successful, zilebesiran could provide a more convenient and effective treatment option for individuals with hypertension.

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