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Impact of IONIS-AGT-Lrx on RAAS Pathway Inhibition and Blood Pressure Control: Promising Results from Phase 2 Trials in Hypertension and Heart Failure

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Introduction

Targeting AGT is a novel approach to inhibit the RAAS pathway. The Renin-Angiotensin-Aldosterone System is a complex physiological system that plays a critical role in the regulation of blood pressure, fluid and electrolyte balance and cardiovascular homeostasis. However, overactivation of the RAAS pathway is implicated in the pathogenesis of hypertension, heart failure and other cardiovascular diseases. Angiotensinogen is a key component of the RAAS pathway, as it serves as a precursor for the generation of angiotensin peptides, including angiotensin II. AGT is primarily synthesized in the liver and is secreted into the circulation, where it is cleaved by renin to generate Ang I, which is subsequently converted to Ang II by Angiotensin-Converting Enzyme [1].

Description

Given the crucial role of AGT in the RAAS pathway, targeting AGT represents a promising strategy for inhibiting RAAS activation and treating hypertension and heart failure. One such approach involves the use of antisense oligonucleotides ASOs directed against AGT. IONIS-AGT-LRx is an ASO directed to hepatocyte-derived AGT. It acts by binding to the mRNA encoding AGT and preventing its translation into protein, thereby reducing the production of AGT. This leads to a reduction in circulating AGT levels, which in turn results in decreased activation of the RAAS pathway [2]. Clinical trials of IONIS-AGT-LRx have shown promising results. In two phase 2 trials, IONIS-AGT-LRx was well tolerated and led to a significant reduction in plasma AGT levels. In one trial, IONIS-AGT-LRx was tested as monotherapy in patients with hypertension and in the other trial, it was tested as an add-on to 2-3 medications for hypertension. In both trials, IONIS-AGT-LRx was shown to effectively lower blood pressure. The development of IONIS-AGT-LRx represents an exciting advancement in the treatment of hypertension and heart failure. By targeting AGT, this novel approach inhibits the RAAS pathway and offers a potentially safer and more effective alternative to current RAAS inhibitors, such as ACE inhibitors and angiotensin receptor blockers [3].

Targeting AGT with ASOs such as IONIS-AGT-LRx represents a promising approach to inhibiting the RAAS pathway and treating hypertension and heart failure. As more clinical trials are conducted, it will be interesting to see how this novel therapy compares to current treatments and whether it offers any additional benefits. In 2 phase 2 trials, IONIS-AGT-LRx has shown promising results as a potential treatment for hypertension and heart failure. This antisense oligonucleotide ASO therapy is directed against angiotensinogen, a key component of the renin-angiotensin-aldosterone system pathway that plays a critical role in the regulation of blood pressure and cardiovascular homeostasis [4].

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In the first trial, IONIS-AGT-LRx was tested as monotherapy in patients with hypertension. The trial included 63 patients with moderate-to-severe hypertension who were not currently taking any antihypertensive medication. The patients were randomized to receive either IONIS-AGT-LRx or placebo for a period of 12 weeks. The results of the trial showed that IONIS-AGT-LRx was well tolerated and led to a significant reduction in plasma AGT levels. Specifically, treatment with IONIS-AGT-LRx led to a 50% reduction in plasma AGT levels compared to placebo. In addition, IONIS-AGT-LRx was associated with a significant reduction in systolic blood pressure, with a mean reduction of 15 mmHg compared to placebo.

In the second trial, IONIS-AGT-LRx was tested as an add-on to 2-3 medications for hypertension. The trial included 62 patients with uncontrolled hypertension who were already taking 2-3 antihypertensive medications. The patients were randomized to receive either IONIS-AGT-LRx or placebo for a period of 12 weeks. The results of this trial were also promising. Treatment with IONIS-AGT-LRx led to a significant reduction in plasma AGT levels, with a mean reduction of 69% compared to placebo. In addition, IONIS-AGT-LRx was associated with a significant reduction in both systolic and diastolic blood pressure, with a mean reduction of 10.6 mmHg and 7.3 mmHg, respectively [5].

Conclusion

Importantly, IONIS-AGT-LRx was well tolerated in both trials, with no serious adverse events reported. The most common adverse events were mild injection site reactions, which were reported in both the treatment and placebo groups. Based on these promising results, IONIS-AGT-LRx is being developed as a potential treatment for hypertension and heart failure. Inhibiting the RAAS pathway by targeting AGT with ASOs represents a novel and potentially safer approach to treating these conditions compared to current RAAS inhibitors, such as ACE inhibitors and angiotensin receptor blockers. Overall, the results of these two phase 2 trials suggest that IONIS-AGT-LRx may be an effective and well-tolerated therapy for hypertension and heart failure. As further clinical trials are conducted, it will be interesting to see how IONIS-AGT-LRx compares to current treatments and whether it offers any additional benefits.

Acknowledgement

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Conflict of Interest

None.

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