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Hot from the hypertensive press
Short analysis of clinical studies that may change our practices in the field of hypertension
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Is there a silver lining on the horizon to overcome medication non-adherence?

Non-adherence to antihypertensive therapy is a major obstacle to optimal blood pressure (BP) control. Renal denervation is one option to overcome this barrier because of an always-on effect of the denervation; recent guidelines upgraded the recommendation for this therapy in selected cases. In the future, another interesting possible option might be small interfering RNA molecules that interfere with targeted RNA of specific proteins. Such an agent, zilebesiran, was designed to achieve long-lasting reduction of angiotensinogen production by liver cells and was examined in a phase 1 study presented in this short letter [1]. Besides the application interval of several months (thus reducing medication non-adherence), possible advantages might include the preserved extrahepatic angiotensinogen expression due to hepatocyte-targeted delivery of the therapeutic agent reducing possible side effects.
The study consisted of several parts and was conducted at four sites in the United Kingdom. Part A was a double-blind, randomized, placebo-controlled study of a single ascending dose of subcutaneous zilebesiran (10, 25, 50, 100, 200, 400 or 800mg). Study participants (n=56 in the different zilebesiran dosing groups, n=28 in the placebo group) had to be between 18 to 65 years of age with treated or untreated hypertension and a mean seated systolic BP (SBP) of 130 to 165mmHg and a mean SBP of>130mmHg as assessed by 24h-BP-measurement. Patients with a secondary cause of hypertension, diabetes or previous cardiovascular events were excluded. The study was sponsored by Alnylam Pharmaceuticals.
Adverse events (the primary endpoint) were numerically less common in the zilebesiran group compared to the placebo group. Nevertheless, mild injection-related side reactions were observed in 9% of the zilebesiran treated patients (vs 0% in the placebo group). Reassuringly, no hypotension, hyperkaliemia or worsening of renal function was reported. Zilebesiran doses of 100mg or more corresponded with mean decreases in serum angiotensinogen levels of more than 90% that were sustained from week 3 through week 12 (secondary endpoint). Decreases in SBP >10mmHg were seen after single doses of zilebesiran of 200mg or more, and the observed change in the mean SBP at week 24 in the 800mg group was -22.5+/-5.1mmHg (exploratory endpoint).
Comment: Phase 1 studies are performed to test the safety profile rather than the efficacy. That the serious adverse events are similarly infrequent as in the placebo group is reassuring. Clearly the study is too small and of too a short duration to assess uncommon serious side effects. The BP lowering effects are encouraging and not dependent on patient adherence once the injection has been performed, which gives hope for the treatment of the significant proportion of non-adherent hypertensive patients.

Reference:

1. Desai, A.S., et al., *Zilebesiran, an RNA Interference Therapeutic Agent for Hypertension.* N Engl J Med, 2023. **389**(3): p. 228-238.

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