Schweizerische Hypertonie-Gesellschaft
Société Suisse d'Hypertension
Società Svizzera d'Ipertensione
Swiss Society of Hypertension

Hot from the hypertensive press
Short analysis of clinical studies that may change our practices in the field of hypertension
02/2025

Baxdrostat: a new antihypertensive drug on the horizon?

In February 2023, Freeman MW et al. published the results of a phase 2 trial of a new antihypertensive drug, baxdrostat, in the renowned New England Journal of Medicine.[1] Baxdrostat is an inhibitor of the aldosterone synthase and should therefore reduce blood pressure.

The phase 2 trial was a multicenter, randomized controlled trial, in which 248 patients with treatment-resistant hypertension were randomly assigned to receive baxdrostat (0.5 mg, 1 mg or 2 mg per day) or placebo. The trial found a dose-dependent reduction of systolic blood pressure of -20.3 mmHg (group receiving 2 mg baxdrostat), of -17.5 mmHg (group receiving 1 mg baxdrostat), of -12.1 mmHg (group receiving 0.5 mg baxdrostat), and -9.4 mmHg (group receiving placebo). In 2.2% of the patients receiving 1 or 2 mg of baxdrostat, relevant hyperkalemia (potassium level ≥6.0 mmol/l) was observed, while in the group receiving 0.5 mg of baxdrostat and in the group receiving placebo no such adverse events were observed.

Comment

Baxdrostat is the first drug, which inhibits aldosterone synthase. Therefore, it can be regarded as the first representative of a new class of antihypertensive drugs. As was to be expected, when a drug decreases aldosterone levels, blood pressure falls – and, as was also to be expected, if aldosterone levels decrease, the risk of hyperkalemia, which is a potentially dangerous complication, increases. In this regard, baxdrostat is not very different in its effect as compared to the drugs already available on the market that block the effect of aldosterone on the mineralocorticoid receptor, such as the steroidal spironolactone or the nonsteroidal eplerenone and finerenone.

According to the nature of a phase 2 trial, only the surrogate endpoint of blood pressure reduction was investigated in this trial. It remains an open question whether baxdrostat also reduces the relevant endpoints such as mortality and/or non-fatal morbidity (e.g., stroke incidence, heart failure incidence). The current phase 2 trial was underpowered in this regard. Therefore, we must wait until results of a phase 3 trial are available showing significant effects on mortality and/or morbidity, before this drug may be approved for the market by the authorities.

In addition to the pending proof of effectiveness against the relevant mortality and morbidity endpoints, baxdrostat will also have to show that it is superior or at least equivalent to the already available drugs inhibiting the effect of aldosterone on the mineralocorticoid receptor. In this regard, also the price will play a role. The costs for a usual daily dose of spironolactone are approximately 0.3 CHF per day, but has the disadvantage of gynecomastia. Eplerenone or finerenone cost approximately 1.5 to 2 CHF per day and the higher price as compared to spironolactone is justified by the fact that they do not provoke gynecomastia. Baxdrostat will also have to be cost-effective as compared to these long-standing, relatively cheap drugs with proven efficacy.

Moreover, baxdrostat will also be in competition with other new antihypertensive drugs, of which some are distinguished by new mechanism of action, such as zilbesiran, an RNA interference therapeutic agent that has to be injected subcutaneously only twice per year,[2] or aprocitentan, a dual endothelin receptor antagonist.[3]

In summary, baxdrostat is promising new drug, but will not have an easy time asserting itself against the established drugs with similar mechanisms of action or the other new drugs in the pipeline.

References:

1 Freeman MW, Halvorsen YD, Marshall W, Pater M, Isaacsohn J, Pearce C, Murphy B, Alp N, Srivastava A, Bhatt DL, Brown MJ; BrigHTN Investigators. Phase 2 Trial of Baxdrostat for Treatment-Resistant Hypertension. N Engl J Med. 2023;388(5):395-405.

2 Desai AS, Webb DJ, Taubel J, Casey S, Cheng Y, Robbie GJ, Foster D, Huang SA, Rhyee S, Sweetser MT, Bakris GL. Zilebesiran, an RNA Interference Therapeutic Agent for Hypertension. N Engl J Med. 2023;389(3):228-238.

3 Schlaich MP, Bellet M, Weber MA, Danaietash P, Bakris GL, Flack JM, Dreier RF, Sassi-Sayadi M, Haskell LP, Narkiewicz K, Wang JG; PRECISION investigators. Dual endothelin antagonist aprocitentan for resistant hypertension (PRECISION): a multicentre, blinded, randomised, parallel-group, phase 3 trial. Lancet. 2022;400(10367):1927-1937.

Prof. Dr. med. Andreas Schoenenberger, Swiss Society of Hypertension

24.04.2023