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Review

Baxdrostat an Emerging Drug in Hypertension Therapy

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Abstract

Hypertension is a major global contributor to cardiovascular morbidity and mortality, and the management of resistant hypertension (RH) remains particularly challenging. Aldosterone synthase inhibitors (ASIs) represent a novel therapeutic class that lowers blood pressure by reducing aldosterone production. Baxdrostat is a selective ASI that inhibits the CYP11B2 enzyme responsible for aldosterone synthesis without interfering with cortisol production, thereby minimizing hormonal adverse effects. Clinical studies have demonstrated that baxdrostat decreases plasma aldosterone levels in a dose-dependent manner while maintaining normal cortisol concentrations. In the Phase 2 BrigHTN trial, baxdrostat significantly reduced both systolic and diastolic blood pressure in patients with RH, with the 2 mg dose providing the most consistent results. However, the HALO trial reported comparable blood pressure reductions in placebo-treated patients, potentially due to improved adherence to background antihypertensive therapy. Overall, baxdrostat has shown a favorable safety profile, with predominantly mild adverse effects and no clinically significant impact on renal function. It is also considered safe for use alongside other medications, including metformin. Ongoing clinical trials are further evaluating its efficacy in patients with chronic kidney disease and primary hyperaldosteronism. Baxdrostat appears to be a promising treatment option for aldosterone-mediated hypertension, particularly in patients who do not respond adequately to conventional therapies.

Keywords: Hypertension; cardiovascular disease; molecular pathophysiology; mechanisms; complications.

Introduction

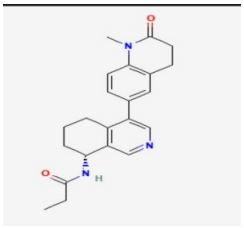
Hypertension remains a major global public health challenge and continues to contribute substantially to cardiovascular (CV) morbidity and mortality as of 2025. It is widely recognized as one of the most significant modifiable risk factors for cardiovascular diseases (CVDs), including coronary heart disease and stroke. Despite considerable advances in hypertension research and the widespread availability of effective antihypertensive therapies, a substantial proportion of individuals fail to achieve adequate blood pressure (BP) control. Consequently, complications associated with uncontrolled hypertension remain highly prevalent worldwide.

Globally, an estimated 55 million deaths were recorded in 2017, of which approximately 17.7 million were attributed to cardiovascular diseases, underscoring the urgent need to better understand and monitor the relationship between modifiable risk factors and mortality. This burden is not uniformly distributed and varies considerably according to the level of economic development, thereby influencing the design and implementation of effective prevention strategies. Revealing trends in years of life lost (YLL) between 2007 and 2017 further highlight this concern, with YLL due to coronary heart disease increasing by 17.3% and those due to stroke rising by 12%.

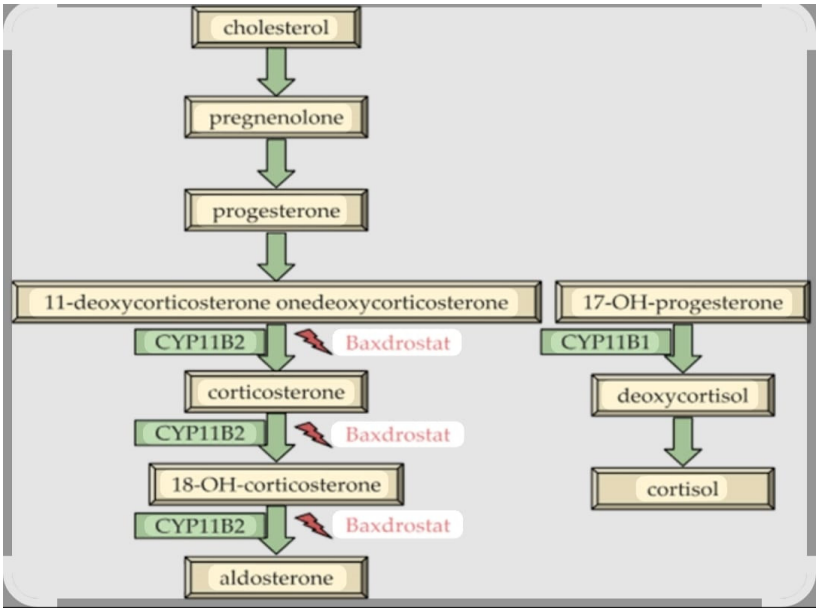
Moreover, blood pressure demonstrates a continuous, graded association with cardiovascular risk across all age groups, with earlier onset hypertension linked to increased cardiovascular mortality and a higher likelihood of end-organ damage.

Current management strategies for hypertension include both non-pharmacological and pharmacological interventions. Lifestyle modification remains the cornerstone of initial therapy, particularly for individuals with newly diagnosed or mildly elevated blood pressure, and encompasses weight reduction, adoption of a low-sodium and potassium-rich diet, regular physical activity, and moderation or cessation of alcohol consumption [6]. When lifestyle interventions are insufficient to achieve target blood pressure goals, or when patients present with elevated atherosclerotic cardiovascular disease risk, pharmacological therapy is recommended.

Structure



Mechanism of action



Baxdrostat exerts its antihypertensive effects through highly selective inhibition of aldosterone synthase (CYP11B2), the key enzyme responsible for aldosterone biosynthesis in the adrenal cortex. Importantly, this selectivity minimizes interference with cortisol synthesis mediated by the closely related enzyme CYP11B1. By selectively reducing aldosterone production, baxdrostat decreases renal sodium and water retention, leading to reduced intravascular volume and a clinically meaningful reduction in blood pressure. These effects are particularly pronounced in patients with resistant or difficult-to-control hypertension.

Adverse Effects

- Electrolyte imbalance
- Hyper kalemia
- Hyponatremia
- **Electolyte shifts:** Most frequent or elevated potassium(hyperkalemia) and decresed sodium(hyponatremia).
- **Neurological:** Headache, dizziness,and fatigue.
- **Musculoskeletal:** Muscle spams.
- **Other:** Urinary tract infections.

Drug interactions

Baxdrostat, a **selective aldosterone synthase inhibitor**, has demonstrated **good tolerability when used with commonly prescribed antihypertensive agents**.

- **Metformin:**
  Available data indicate **no clinically meaningful pharmacokinetic interaction** between baxdrostat and metformin. Co-administration is generally considered safe, and **dose adjustment is not routinely required**.
- **Potassium-Raising Medications:**
  Caution is advised when baxdrostat is used with **potassium-sparing diuretics, ACE inhibitors, angiotensin receptor blockers (ARBs), or potassium supplements**, due to the **additive risk of hyperkalemia** associated with aldosterone pathway inhibition. Regular monitoring of serum potassium is recommended.
- **NSAIDs:**
  Nonsteroidal anti-inflammatory drugs may impair renal potassium excretion and increase the risk of hyperkalemia. Concomitant use with baxdrostat should be approached with caution**,** particularly in patients with reduced renal function or other risk factors, with appropriate laboratory monitoring.

Uses

Baxdrostat is a novel, selective aldosterone synthase inhibitor developed for the management of uncontrolled and resistant hypertension.

- **Resistant Hypertension:** Demonstrates significant efficacy in patients with persistently elevated blood pressure despite treatment with three or more antihypertensive agents, including a diuretic.
- **Uncontrolled Hypertension:** Provides meaningful blood pressure reductions in difficult-to-treat cases, improving overall blood pressure control and potentially reducing the risk of major cardiovascular events such as stroke and myocardial infarction.
- **Primary Aldosteronism:** Currently under investigation for its ability to selectively suppress aldosterone production, offering a targeted therapeutic approach in patients with aldosterone-driven hypertension.
- **Sustained 24-Hour Blood Pressure Control:** Produces consistent reductions in both daytime and nocturnal blood pressure, addressing nocturnal and early-morning hypertension patterns associated with increased cardiovascular risk.
- **Chronic Kidney Disease (CKD):** Being investigated for potential benefits in patients with CKD, particularly where aldosterone excess contributes to disease progression.
- **Therapeutic Role:** Offers a novel treatment option for patients who do not respond adequately to conventional antihypertensive regimens.

Contraindications

Baxdrostat has no formally established absolute contraindications to date. However, several patient populations were excluded from clinical trials, and these factors should be considered important precautions in clinical use:

- **Hyperkalemia:**
  Baxdrostat may increase serum potassium levels. In clinical studies, hyperkalemia was typically managed with dietary modification, monitoring, or temporary treatment interruption. Patients with baseline hyperkalemia were excluded from trials.
- **RenalImpairment:**
  Patients with **moderate to severe kidney dysfunction** (eGFR < 45 mL/min/1.73 m^2) were not included in studies, due to increased risk of potassium elevation and limited safety data.
- **Severe Hypertension:**
  Individuals with **severely uncontrolled blood pressure** (≥180/110 mmHg) were excluded from trials.
- **Cardiac Conditions:**
  Patients with a history of long QT syndrome, significant heart block, complex arrhythmias, or sudden cardiac death were excluded, reflecting potential safety concerns in these populations.
- **Concomitant Medications:**
  Recent use of **mineralocorticoid receptor antagonists (MRAs)**, **potassium-sparing diuretics**, or certain **antiarrhythmic agents** led to exclusion in trials, due to overlapping effects on potassium balance or cardiac conduction.

Conclusion

Baxdrostat represents the first highly selective, competitive inhibitor of aldosterone synthase developed for the treatment of resistant hypertension. Patients who remain hypertensive despite receiving multiple antihypertensive agents may particularly benefit from this novel therapeutic approach. Current clinical evidence demonstrates that baxdrostat effectively lowers blood pressure while maintaining a favorable and generally well-tolerated safety profile. Ongoing and future studies are expected to further clarify its long-term efficacy, safety, and durability of blood pressure control, as well as to expand understanding of its potential role in additional aldosterone-mediated cardiovascular and renal conditions.

Arterial hypertension remains a major modifiable risk factor for cardiovascular disease and continues to be challenging to control effectively despite advances in diagnostic and therapeutic strategies. Adrenal hormones, particularly aldosterone, play a central role in the pathophysiology of hypertension, and targeted modulation of this pathway represents a promising therapeutic approach, especially in patients with resistant disease. Baxdrostat is a novel, highly selective inhibitor of aldosterone synthase (CYP11B2) that effectively reduces aldosterone production without significantly impairing cortisol synthesis.

Importantly, its efficacy and safety profile have also been observed in patients with impaired renal function. Ongoing phase 3 clinical trials, including studies in diverse and Asian populations, are expected to further define its long-term effectiveness, safety, and potential role in the broader management of aldosterone-mediated cardiovascular and renal disorders.

- **Company conducting phase 3 trials of baxdrostat is Astrazeneca**

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