Hereditary Angioedema Prophylaxis: Weighing Berotralstat and Lanadelumab's Safety

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Managing hereditary angioedema (HAE) effectively requires careful consideration of available prophylactic therapies, particularly the kallikrein inhibitors berotralstat and lanadelumab. While both treatments aim to reduce attack frequency, understanding their distinct safety profiles is crucial for tailoring individualized patient care.

KEY TAKEAWAYS

- The Pivot: Retrospective data highlights the practical importance of proactive adverse effect monitoring and considering pre-existing conditions when selecting berotralstat or lanadelumab for hereditary angioedema prophylaxis.
- The Data: While generally mild to moderate, gastrointestinal issues such as abdominal pain, diarrhea, and nausea are the most commonly reported adverse events for berotralstat.
- The Action: Clinicians should engage in shared decision-making early, thoroughly discussing the distinct safety profiles of berotralstat (e.g., GI side effects, CYP3A4 interactions) and lanadelumab (e.g., injection site reactions, rare hypersensitivity) with patients, and considering individual patient histories.

Guideline Alignment

Current guidelines, such as those from the AAAAI (American Academy of Allergy, Asthma & Immunology) and EAACI (European Academy of Allergy and Clinical Immunology), recommend C1-inhibitors, kallikrein inhibitors (berotralstat and lanadelumab), and selective bradykinin B2 receptor antagonists (icatibant) for HAE management. These guidelines emphasize individualized treatment plans based on disease severity, attack frequency, patient preference, and accessibility. The retrospective data adds a layer of practical consideration, emphasizing proactive adverse effect monitoring. If anything, it encourages providers to lean into shared decision-making early.

Comparative Safety Profiles

Berotralstat, as an oral medication, offers convenience, potentially improving adherence for some patients. However, it's not without potential drawbacks. The most commonly reported adverse events include abdominal pain, diarrhea, and nausea. While generally mild to moderate, these gastrointestinal issues can impact quality of life and may lead to discontinuation in some cases. Furthermore, drug-drug interactions should be carefully evaluated, as berotralstat is metabolized by CYP3A4.

Lanadelumab, administered via subcutaneous injection every two or four weeks, has a different safety profile.1 Injection site reactions are common, though usually self-limiting. Of greater concern is the potential for hypersensitivity reactions,

including anaphylaxis, although these are rare. The long-term immunogenicity of lanadelumab is still being studied, and the development of anti-drug antibodies could potentially reduce its efficacy over time.1

This retrospective study highlights the importance of considering pre-existing conditions when selecting a prophylactic agent. For instance, patients with a history of gastrointestinal disorders may be less tolerant of berotralstat, while those with a history of allergic reactions may be at higher risk with lanadelumab. Careful patient selection and proactive monitoring are essential to mitigate potential risks.

Study Limitations

Retrospective studies are inherently limited by their design. Data collection relies on accurate record-keeping, and the lack of randomization introduces the potential for selection bias. The sample size may be insufficient to detect rare but serious adverse events. Moreover, the study population may not be fully representative of all HAE patients, limiting the generalizability of the findings. Confounding variables, such as concomitant medications or other medical conditions, may not be adequately controlled for, further complicating the interpretation of the results. Always take reported p-values with a grain of salt.

Patient Counseling

Shared decision-making is paramount in HAE management. Patients need to be fully informed about the benefits and risks of each prophylactic option. For berotralstat, emphasize the importance of adherence and potential gastrointestinal side effects. Provide strategies for managing these side effects, such as taking the medication with food or using over-the-counter remedies. For lanadelumab, educate patients on proper injection technique and the signs and symptoms of allergic reactions. Instruct them to carry an epinephrine auto-injector and seek immediate medical attention if anaphylaxis occurs. Discuss the potential for long-term immunogenicity and the importance of regular follow-up appointments.1

Furthermore, the long-term safety and efficacy data for both berotralstat and lanadelumab are still evolving, necessitating ongoing post-marketing surveillance and real-world evidence generation.1 Clinicians should remain vigilant for emerging adverse events and consider participating in registries to contribute to a broader understanding of these therapies.

Future Directions and Research Gaps

The comparative safety profiles of berotralstat and lanadelumab, while elucidated by this retrospective analysis, underscore several critical areas for future research and clinical development in HAE prophylaxis. A primary gap lies in the absence of head-to-head randomized controlled trials (RCTs) directly comparing these two agents. Such trials would provide the highest level of evidence regarding their relative efficacy, safety, and impact on patient-reported outcomes, moving beyond the inherent limitations of observational studies.

Further investigation into patient subgroups is also warranted. For instance, understanding the optimal prophylactic strategy for pediatric patients, pregnant individuals, or those with significant comorbidities (e.g., severe renal or hepatic impairment, autoimmune diseases) remains an area of unmet need. Real-world data, collected through robust registries

and large-scale observational studies, will be crucial in characterizing the long-term safety and effectiveness of these drugs in diverse patient populations, particularly concerning rare adverse events and the development of anti-drug antibodies for lanadelumab.1 Research into predictive biomarkers that could guide personalized treatment selection, identifying patients most likely to respond to or tolerate a specific therapy, would represent a significant advance in HAE management.

Moreover, the economic implications and cost-effectiveness of these prophylactic treatments need continued evaluation. While both berotralstat and lanadelumab significantly reduce attack frequency, their high cost necessitates careful consideration within healthcare systems. Future research should explore the impact of improved prophylaxis on overall healthcare resource utilization, including emergency department visits and hospitalizations, to provide a comprehensive understanding of their value. This will inform policy decisions and ensure equitable access to effective HAE treatments.

Finally, patient preference and quality of life should remain central to future research. Studies incorporating patient-reported outcome measures (PROMs) that capture the burden of treatment, convenience, and overall satisfaction will be invaluable. Understanding how different administration routes (oral vs. subcutaneous) and dosing frequencies influence adherence and patient well-centric outcomes will further refine treatment algorithms and enhance shared decision-making in HAE prophylaxis.

CLINICAL IMPLICATIONS

The retrospective comparison of berotralstat and lanadelumab highlights a crucial point for HAE management: convenience should not overshadow individualized risk assessment. While oral berotralstat offers ease of administration, its gastrointestinal adverse events can significantly impact patient quality of life and adherence. This means clinicians must proactively discuss these potential issues and provide management strategies from the outset. Early, open communication is key to maintaining patient engagement with their prophylactic therapy.

For industry, specifically companies like BioCryst Pharmaceuticals and Takeda, these real-world insights are invaluable. They underscore the need for continued post-marketing surveillance and the generation of robust long-term safety data. The potential for drug-drug interactions with berotralstat and the long-term immunogenicity of lanadelumab remain areas requiring further investigation. Future research should prioritize head-to-head randomized controlled trials to provide definitive comparative safety and efficacy profiles, addressing the inherent limitations of retrospective analyses.

Patients with HAE deserve to be full partners in their treatment decisions. Clinicians must move beyond simply presenting options and instead engage in shared decision-making, considering not just guideline recommendations from bodies like the AAAAI and EAACI, but also a patient's medical history, lifestyle, and preferences. For instance, a patient with pre-existing GI issues might find lanadelumab's injection site reactions more tolerable than berotralstat's abdominal discomfort. Conversely, needle-averse patients might prefer the

> oral route despite potential GI side effects. This nuanced approach ensures that the chosen prophylaxis aligns with the patient's specific needs and improves the likelihood of sustained adherence.

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