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The Evolving Therapeutic Landscape for Hereditary Angioedema in Canada: Clinical Advances and Unmet Needs

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Hereditary angioedema (HAE) is a rare genetic disorder characterized by recurrent, potentially life-threatening episodes of swelling due to bradykinin overproduction. Advances in the understanding of molecular pathophysiology, coupled with the development of innovative therapies, are transforming the management of HAE. This underscores the need for strategic planning to incorporate emerging treatment modalities into the Canadian therapeutic framework for HAE.

Introduction

HAE typically presents with recurrent episodes of non-pitting, non-pruritic swelling, commonly involving the skin, gastrointestinal tract, and upper airway. Symptoms generally start in childhood or adolescence and can have a significant impact on quality of life and mental health. Cutaneous attacks can be disfiguring and painful, often affecting the face, extremities, or genitals. Abdominal attacks present with bloating, severe cramping, vomiting, and diarrhea, and may be mistaken for an acute surgical abdomen. Laryngeal attacks necessitate immediate medical attention due to the risk of asphyxiation. Although HAE is estimated to affect 1 in 50,000 individuals,[1] it is likely underdiagnosed in Canada.

Pathophysiology of Hereditary Angioedema

HAE is primarily driven by bradykinin overproduction due to dysregulation of the contact system. Unlike histamine-mediated angioedema, bradykinin-mediated HAE does not respond to antihistamines, corticosteroids, or epinephrine, making accurate differentiation essential for appropriate diagnosis and treatment.[2] In HAE Types I and II, mutations in the *SERPING1* gene lead to either reduced (Type I) or dysfunctional (Type II) C1 esterase inhibitor (C1-INH), resulting in uncontrolled plasma kallikrein activation and excessive bradykinin release. Bradykinin, a potent vasodilator, increases vascular permeability. In HAE with normal C1-INH (nC1-INH), mutations in genes such as *F12, PLG, ANGPT1, KNG1, MYOF,* and *HS3ST6* have been implicated, though the underlying mechanisms are not fully elucidated.[3] Advances in understanding HAE pathophysiology have enabled the development of targeted therapies that inhibit bradykinin synthesis or activity.

Current Standard of Care in Canada

Hereditary angioedema presents a unique clinical challenge due to its unpredictable and debilitating attacks, limited conventional treatment options, and frequent misdiagnosis. The International/Canadian Hereditary Angioedema Guideline (2019) emphasizes the importance of individualized patient care, advocating for the use of on-demand treatments to treat acute attacks and consideration of long-term prophylaxis for patients with frequent or severe episodes.[4] The selection of a treatment strategy is influenced by various factors, including the patient's history of attack location, severity and frequency, HAE subtype, access to emergency care and individual preferences.

On-Demand Therapies Currently Available in Canada:

Icatibant (Firazyr) acts as a selective competitive antagonist of the bradykinin B2 receptor, preventing the binding of bradykinin to its receptor. Icatibant is approved for self-administration during acute HAE attacks. The FAST-3 trial demonstrated that icatibant significantly reduced the time to symptom relief in acute HAE attacks, with a median time of two hours to achieve a 50% reduction in symptoms versus 19.8 hours with placebo (P<0.001).[5] Icatibant is well tolerated, with mild and transient injection-site reactions being the most common side effect.

Plasma-derived C1-INH (Berinert) is used to replenish deficient or dysfunctional C1-INH, administered through intravenous infusion to rapidly increase intravascular C1-INH levels. Berinert is widely used and available for home infusion in Canada. In a randomized, double-blind, placebo-controlled trial, Berinert (20 U/kg) significantly accelerated symptom relief in acute abdominal or facial HAE attacks, with a median time to onset of relief of 0.5 hours versus 1.5 hours with placebo (P=0.0025).[6] Berinert also reduced the median time to complete symptom resolution from 7.8 to 4.9 hours (P=0.0024).[6] While Berinert is generally well tolerated, its intravenous administration may pose challenges for some patients, particularly those with difficult venous access or needle phobia. Additionally, home infusion of Berinert may be inappropriate for patients with infrequent attacks due to limited opportunities to maintain self-administration proficiency.

Fresh frozen plasma (FFP) contains C1-INH and may be used for treating acute attacks when other HAE-specific therapies are unavailable. However, FFP cannot be used for home administration and may be associated with an increased risk of adverse effects, including volume overload and worsening angioedema since FFP contains substrates that may further activate complement.

Prophylactic Therapies Currently Available in Canada:

Lanadelumab (Takhzyro) is a recombinant, fully human monoclonal antibody that inhibits plasma kallikrein and is administered subcutaneously every 2 to 4 weeks. During the HELP trial, lanadelumab significantly reduced HAE attack rates, with the most effective dose (300 mg every 2 weeks) achieving a mean of 0.26 attacks/month versus 1.97 attacks/month with placebo (p<0.001).[7] Up to 76.9% of lanadelumab-treated patients remained attack-free, and quality-of-life scores improved significantly during the study period.[7] The most common side effects consist of mild, self-limited injection-site reactions.

Subcutaneous plasma-derived C1-INH (Haegarda) is a volume-reduced pdC1-INH concentrate that provides sustained C1-INH levels.

In a phase 2 open-label study, twice-weekly administration of Haegarda resulted in dose-dependent increases in functional C1-INH activity, with mean modelled trough levels of 31.7%, 44.3%, and 80.5% for the 1500 IU, 3000 IU, and 6000 IU doses, respectively.[8] Higher doses achieved protective C1-INH levels (>40%), were associated with fewer breakthrough attacks, and demonstrated a favourable safety profile.[8]

Berotralstat (Orladeyo) is an oral kallikrein inhibitor that is taken once daily, offering a convenient administration option. In the APeX-2 Part 3 trial, a daily dose of 150 mg of berotralstat reduced the mean monthly HAE attack rates by 90.8% at 96 weeks (2 years).[9] Berotralstat is generally well tolerated, although mild transient gastrointestinal side effects can occur. Patient-reported outcomes indicated improved quality of life and increased treatment satisfaction.[9]

A systematic review of 63 studies has confirmed that attenuated androgens (e.g., danazol, stanozolol) are effective for long-term prophylaxis. Placebo-controlled trials have shown that these treatments can reduce attack rates from over 90% with placebo to as low as 2% with danazol.[10] However, long-term use of these androgens is associated with dose- and duration-related adverse effects, including weight gain, menstrual irregularities, virilization, hepatic enzyme changes, and rare cases of hepatic tumours. This warrants cautious, individualized use and regular monitoring. Due to the high rate of adverse effects, androgens are now only considered for selected patients, at the lowest effective dose, as a second-line therapy.

Antifibrinolytics (e.g., tranexamic acid) are not recommended for long-term prophylaxis in HAE. However, they have been shown to reduce the frequency and severity of HAE attacks in small cohorts of patients.[11] Tranexamic acid is a less potent but better-tolerated alternative to attenuated androgens in select patients with HAE and may be considered when other HAE-specific therapies are unavailable.

Emerging Therapies

Emerging treatments for HAE are designed to enhance efficacy, improve ease of use, and provide sustained disease control. While some therapies are in the advanced stages of clinical development, they are currently only accessible in Canada through clinical trials. The commercial availability of these therapies will expand treatment options and support personalized HAE management, in line with the International/Canadian HAE Guidelines. The emergence of oral therapies, extended-interval therapies, and gene editing holds promise for optimizing disease control and reducing the healthcare burden for individuals with HAE in Canada.

Garadacimab is a subcutaneously administered monoclonal antibody that targets activated Factor XII, thereby inhibiting the kallikrein-kinin cascade. In the phase 3 VANGUARD trial, garadacimab (200 mg monthly) reduced the mean monthly hereditary angioedema attack rate by 87% compared to placebo (0.27 versus 2.01 attacks; P<0.0001). Additionally, 62% of garadacimab-treated patients remained attack-free over 6 months.[12] Garadacimab is currently under review by Health Canada and the Canada Drug Agency.

Donidalorsen is an antisense oligonucleotide that reduces the production of plasma prekallikrein by inhibiting prekallikrein mRNA and is administered subcutaneously. In a phase 2 open-label extension study, donidalorsen achieved a 96% reduction in attack rates over 2 years, with favourable quality of life outcomes.[13] The treatment was well tolerated and demonstrated flexible dosing, allowing administration every 4 or 8 weeks.[13]

Deucrictibant (PHVS416) is an oral bradykinin B2 receptor antagonist currently under investigation for both on-demand and long-term prophylactic use. The phase 2 RAPIDe-1 trial indicated significantly improved HAE symptoms across all doses of deucrictibant (10, 20, and 30 mg), with a median time to ≥30% symptom reduction of 2.1–2.7 hours compared to 8.0 hours with placebo (p<0.0001).[14] In the CHAPTER-1 trial, which evaluated deucrictibant for prophylaxis, daily doses of 20 mg and 40 mg reduced monthly attack rates by 79.3% and 84.5%, respectively, compared with placebo.[15]

Sebetralstat (KVD900) is an oral plasma kallikrein inhibitor with the potential to be the first oral on-demand therapy for HAE. In a phase 3 trial, oral sebetralstat at doses of 300 mg and 600 mg significantly shortened the median time to symptom relief during HAE attacks to 1.61 and 1.79 hours, respectively, compared to 6.72 hours with placebo (P<0.001 and P=0.001).[16] Additionally, it demonstrated higher complete resolution rates at 24 hours (42.5% [300 mg dose]

and 49.5% [600 mg dose] versus 27.4% [placebo]) with a favourable safety profile.[16]

Navenibart (STAR-0215) is a long-acting monoclonal antibody administered subcutaneously that inhibits plasma kallikrein. A recently published phase 1a study indicated that navenibart was well tolerated in healthy adults and achieved up to 85% inhibition of plasma kallikrein activity ($P<0.001$).[17] The study also demonstrated a mean half-life of 82–106 days for doses ≥300 mg, supporting the feasibility of subcutaneous administration every 3 to 6 months.[17]

ATN-249 is an orally-administered prekallikrein inhibitor being developed for prophylactic use in HAE. Preclinical studies have demonstrated that ATN-249 provides 10-fold greater relative plasma kallikrein inhibition compared to C1-INH.[18]

NTLA-2002 is a CRISPR/Cas9-based gene-editing therapy that targets the *KLKB1* gene, aiming to disrupt the hepatic expression of plasma prekallikrein by inactivating the gene encoding kallikrein B1. A single intravenous dose of NTLA-2002 led to dose-dependent reductions in plasma kallikrein levels ranging from 67% to 95%, and a mean 95% reduction in monthly angioedema attack frequency, with no serious adverse events observed in the phase 1 trial.[19] In the phase 2 trial, NTLA-2002 at doses of 25 mg and 50 mg reduced the mean monthly angioedema attack rate by 75% and 77%, respectively, compared to placebo. Notably, 73% of patients receiving the 50 mg dose remained attack-free over the 16-week treatment period.[20]

BMN 331 is an AAV5-based gene therapy designed to transduce the *SERPING1* gene into hepatocytes, enabling patients to produce functional C1-INH. A phase 1/2, single-arm, open-label, dose-escalation and dose-expansion study of BMN 331 is currently under way.[21]

Unmet Needs In HAE Management in Canada

Despite significant therapeutic advancements, critical gaps in the management of hereditary angioedema persist. Addressing these challenges is essential to optimizing outcomes and achieving high-quality care that aligns with current clinical guidelines.

- Many patients experience a diagnostic delay of approximately 10 years from symptom onset, often experiencing multiple misdiagnoses, including allergic, gastrointestinal, or psychiatric conditions, which can lead to unnecessary suffering, inappropriate treatment, and avoidable morbidity.[22]
- While the adoption of virtual care can improve access to HAE expertise, physical access to infusion services, emergency care, or trained healthcare providers remains a challenge, particularly in rural and northern regions.
- The absence of robust data and standardized treatment strategies for certain subpopulations, such as pediatric HAE patients and HAE with normal C1-INH, has led to limited therapeutic options for these groups.
- The unpredictability of attacks and the burden of living with a complex, congenital disease contribute to anxiety, depression, and social isolation for HAE patients. Mental health support for HAE is often lacking, potentially leading patients to feel misunderstood or dismissed by healthcare providers.
- Not all patients are eligible or able to access the currently available HAE-specific therapies due to cost or coverage limitations.
- National data on HAE prevalence, treatment patterns, and outcomes are scarce. A centralized patient registry and prospective real-world evidence initiatives would support better clinical understanding and inform health policy decisions for Canadian patients with HAE, particularly in the era of novel therapies.

Conclusion

The therapeutic landscape for HAE is expanding beyond traditional intravenous and subcutaneous therapies. Emerging therapies hold promise for more effective, convenient, and personalized care for HAE patients in Canada. Patient-centric innovations such as oral agents, gene editing, and quarterly or biannual injections may transform care. However, these advancements will require shared decision-making and patient engagement. Additionally, real-world and long-term safety data will be required to guide the integration of emerging and novel therapies into routine HAE practice.

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References

1. Busse PJ, Christiansen SC, Riedl MA, Banerji A, Bernstein JA, Castaldo AJ, et al. US HAEA Medical Advisory Board 2020 guidelines for the management of hereditary angioedema. J Allergy Clin Immunol Pract. 2021;9(1):132-150.e3. doi:10.1016/j.jaip.2020.08.046
2. Maurer M, Magerl M, Betschel S, Lumry W, Li HH, Longhurst H, et al. The international WAO/EAACI guideline for the management of hereditary angioedema – The 2021 revision and update. World Allergy Organ J. 2022;15(3):100627. doi:10.1016/j.waojou.2022.100627
3. Santacroce R, D'Andrea G, Maffione AB, Margaglione M, d'Apolito M. The genetics of hereditary angioedema: a review. J Clin Med. 2021;10(9):2023. doi:10.3390/jcm10092023
4. Betschel S, Badiou J, Binkley K, Borici-Mazi R, Hébert J, Kanani A, et al. The International/Canadian Hereditary Angioedema Guideline. Allergy Asthma Clin Immunol. 2019;15:72. doi:10.1186/s13223-019-0376-8
5. Lumry WR, Li HH, Levy RJ, Potter PC, Farkas H, Moldovan D, et al. Randomized placebo-controlled trial of the bradykinin B2 receptor antagonist icatibant for the treatment of acute attacks of hereditary angioedema: the FAST-3 trial. Ann Allergy Asthma Immunol. 2011;107(6):529-537. doi:10.1016/j.anai.2011.08.015
6. Craig TJ, Levy RJ, Wasserman RL, Bewtra AK, Hurewitz D, Obtulowicz K, et al. Efficacy of human C1 esterase inhibitor concentrate compared with placebo in acute hereditary angioedema attacks. J Allergy Clin Immunol. 2009;124(4):801-808. doi:10.1016/j.jaci.2009.07.017.
7. Banerji A, Riedl MA, Bernstein JA, Cicardi M, Longhurst H, Zuraw BL, et al. Effect of lanadelumab compared with placebo on prevention of hereditary angioedema attacks: a randomized clinical trial. JAMA. 2018;320(20):2108-2121. doi:10.1001/jama.2018.16773
8. Zuraw BL, Cicardi M, Longhurst HJ, Bernstein JA, Li HH, Magerl M, et al. Phase II study results of a replacement therapy for hereditary angioedema with subcutaneous C1-inhibitor concentrate. Allergy. 2015;70(10):1319-1328. doi:10.1111/all.12658
9. Kiani-Alikhan, Sorena et al. Once-Daily Oral Berotralstat for Long-Term Prophylaxis of Hereditary Angioedema: The Open-Label Extension of the APeX-2 Randomized Trial J Allergy Clin Immunol Pract. 2024 Mar;12(3):733-743.e10. doi: 10.1016/j.jaip.2023.12.019. Epub 2023 Dec 18.
10. Riedl MA. Critical appraisal of androgen use in hereditary angioedema: a systematic review. Ann Allergy Asthma Immunol. 2015;114(4):281-288. doi:10.1016/j.anai.2015.01.003.
11. Sheffer AL, Austen KF, Rosen FS. Tranexamic acid therapy in hereditary angioneurotic edema. N Engl J Med. 1972;287(9):452-454. doi:10.1056/NEJM197208312870907
12. Craig TJ, Reshef A, Li HH, Jacobs JS, Bernstein JA, Farkas H, et al. Efficacy and safety of garadacimab, a factor XIIa inhibitor for hereditary angioedema prevention (VANGUARD): a global, multicentre, randomised, double-blind, placebo-controlled, phase 3 trial. Lancet. 2023;401(10384):1079-1090. doi:10.1016/S0140-6736(23)00350-1
13. Petersen RS, Bordone L, Riedl MA, Tachdjian R, Craig TJ, Lumry WR, et al. A phase 2 open-label extension study of prekallikrein inhibition with donidalorsen for hereditary angioedema. Allergy. 2024;79(3):724-734. doi: 10.1111/all.15948.
14. Maurer M, Anderson J, Aygören-Pürsün E, Lesage A, Lu P, Reidl M, et al. Efficacy and safety of bradykinin B2 receptor inhibition with oral PHVS416 in treating hereditary angioedema attacks: results of RAPIDe-1 phase 2 trial [AAAAI abstract 411]. J Allergy Clin Immunol. 2023;151(2 Suppl I): AB134. https://doi.org/10.1016/j.jaci.2022.12.419
15. Riedl M, Anderson J, Arcoleo F, Cancian M, Chapdelaine H, Conlon N, et al. Efficacy and safety of bradykinin b2 receptor antagonism with oral deucrictibant in prophylaxis of hereditary angioedema attacks: results of CHAPTER-1 phase 2 trial. J Allergy Clin Immunol. 2024;153(2). AB11
16. Riedl MA, Farkas H, AygörenPürsün E, Psarros F, Soteres DF, Staevska M, et al. Oral Sebetralstat for on-demand treatment of hereditary angioedema attacks. N Engl J Med. 2024;391(1):32-43. doi:10.1056/NEJMoa2314192.
17. Lumry W, Gunsior M, Cohen T, Bernard K, Gustafson P, Chung J, et al. Safety and pharmacokinetics of long-acting plasma kallikrein inhibitor navenibart (STAR-0215) in healthy adults. Ann Allergy Asthma Immunol. Published online March 28, 2025. doi:10.1016/j.anai.2025.03.016
18. Attune Pharmaceuticals. Attune pharmaceuticals announces pre-clinical data for ATN-249, an oral plasma kallikrein inhibitor for the treatment of HAE at AAAAI [Internet]. Published 6 March 2017. [cited 9 May 2025]. Available from: https://www.globenewswire.com/news-release/2017/03/06/931801/0/en/Attune-Pharmaceuticals-Announces-Pre-Clinical-Data-for-ATN-249-An-Oral-Plasma-Kallikrein-Inhibitor-for-the-Treatment-of-HAE-at-AAAAI.html
19. Longhurst HJ, Lindsay K, Petersen RS, Fijen LM, Gurugama P, Maag D, et al. CRISPR-Cas9 in vivo gene editing of KLKB1 for hereditary angioedema. N Engl J Med. 2024;390(5):432-441. doi:10.1056/NEJMoa2309149.
20. Cohn DM, Gurugama P, Magerl M, Katelaris CH, Launay D, Bouillet L, et al. CRISPR-based therapy for hereditary angioedema. N Engl J Med. 2025;392(5):458-467. doi:10.1056/NEJMoa2405734.
21. ClinicalTrials.gov Identifier: NCT05121376. A Gene Therapy Study of BMN 331 in Subjects With Hereditary Angioedema (HAErmony-1) [cited 2025 Apr 21]. Available from: https://clinicaltrials.gov/study/NCT05121376
22. Lee EY, Hsieh J, Caballero T, McCusker C, Kanani A, Lacuesta G, et al. Demographic and clinical characteristics of patients with hereditary angioedema in Canada. Ann Allergy Asthma Immunol. 2022;128(1):89-94.e1. doi:10.1016/j.anai.2021.07.015