Clinical Commentary Review

Specific Targeting of Plasma Kallikrein for Treatment of Hereditary Angioedema: A Revolutionary Decade

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Hereditary angioedema (HAE) is a rare, chronic, genetic disease that presents with nonpruritic angioedema of the face, extremities, airway (can be life-threatening), genitourinary system, and abdomen. These symptoms can significantly impair daily activities. Hereditary angioedema is classified into HAE owing to a deficiency of functional C1INH (HAE-C1INH) or HAE with normal C1INH (HAE-nl-C1INH). Both type I and II HAE-C1INH result from inherited or spontaneous mutations in the SERPING1 gene, which encodes for C1INH. These mutations result in C1INH dysfunction, leading to uncontrolled plasma kallikrein activity with excessive bradykinin production. Bradykinin receptor activation leads to vasodilation, increased vascular permeability, and smooth muscle contractions, resulting in submucosal angioedema through fluid extravasation. Hereditary angioedema nl-C1INH is caused by either a known or unknown genetic mutation. The underlying mechanism of HAE-nl-C1INH is less well understood but is thought to be related to bradykinin signaling. Plasma kallikrein inhibitors have been developed to inhibit the kallikrein-kinin pathway to prevent (prophylactic) and treat on-demand (acute) HAE attacks. Several of these medications are delivered through subcutaneous or intravenous injection, although new and emerging therapies include oral formulations. This article provides a historical review and describes the evolving landscape of available kallikrein inhibitors to treat HAE-C1INH. © 2021 The Authors. Published by Elsevier Inc. on behalf of the American Academy of Allergy, Asthma & Immunology. This is an open access article under the CC BY-NC-ND license (http://creativecommons.org/licenses/by-nc-nd/4.0/). (J Allergy Clin Immunol Pract 2022;10:716-22)

Key words: Kallikrein; Kallikrein inhibitor; Hereditary angioedema; Bradykinin

INTRODUCTION

Hereditary angioedema (HAE) is a rare, chronic, heterogeneous disease characterized by unpredictable and potentially life-threatening attacks. Episodes of angioedema are nonpruritic and typically occur in the extremities, face, airway (which can be life-threatening), and genitourinary and gastrointestinal system; the latter can produce severe abdominal pain, nausea, and vomiting.[1,2]

Hereditary angioedema is debilitating and can significantly impair daily activities because of the physical manifestations and emotional consequences of the disease's unpredictable and potentially life-threatening nature. Consequently, patients with HAE report declining quality of life (QoL). Family members and caregivers also experience emotional and physical burdens.[2,3-8] The frequency of attacks is highly variable; 28% of patients report one or more attack per week, 36% report one or more per month but less than one per week, 18% report one or more over 2 or 3 months, and 18% report less than 1 attack over 6 months.[9] Patients are incapacitated for an average of 5.5 days each attack.[6] Many triggers of HAE attacks cannot be identified, although 56% of patients report emotional distress, physical trauma, estrogen, angiotensin-converting enzyme inhibitors, and infection as precipitants.[10]

Hereditary angioedema is classified as HAE with C1INH deficiency or dysfunction (HAE-C1INH) or HAE with normal C1INH (HAE-nl-C1INH). Hereditary angioedema C1INH is the most common form of HAE and is further divided into type I or II HAE.[11-16] Patients with type I HAE have a deficiency of serum C1INH protein levels and C1INH dysfunction. Mutations leading to type II HAE allow for proper gene translation but result in normal or elevated C1INH levels with reduced function.[17,18] To date, over 300 mutations have been identified; these can be inherited in an autosomal dominant manner, or in 15% to 25% of cases, they are de novo.[8,12,17,19] Disease onset of HAE-C1INH commonly occurs in childhood,[3] and the condition affects approximately 1:50,000 people globally.[4,5]

Patients with HAE-nl-C1INH have normal levels of C1INH protein and function but experience similar symptoms of type I and II HAE.[20] In some instances, the underlying genetic mutation can be identified (ie, factor XII,[21] angiopoietin-1,[22]

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Abbreviations used
AE- Adverse events
C1INH- C1 inhibitor protein
FDA- US Food and Drug Administration
HAE- Hereditary angioedema
HAE-nl-C1INH- Hereditary angioedema with normal C1INH
HMWK- High–molecular weight kininogen
pd-C1INH- Plasma-derived C1 inhibitor protein
QoL- Quality of life
TEAE- Treatment-emergent adverse event

plasminogen,[23,24] kininogen-1,[25] myoferlin,[25] and heparan sulfate 3-O-sulfotransferase 6[25]). In other cases, the genetic mutation has not been identified; these cases are referred to as HAE-unknown.[11]

Pathophysiology of HAE: kallikrein-kinin pathway

The pathophysiology of type I and II HAE is primarily driven by overproduction of bradykinin caused by C1INH dysfunction or deficiency,[13] resulting in vascular permeability with fluid extravasation and angioedema.[14] Hereditary angioedema-nl-C1INH is thought to be caused by excessive bradykinin formation except mutant angiopoietin-1, where the defect lies with the endothelial cell.[22] The bradykinin-forming pathway, also referred to as the kallikrein-kinin pathway, has a crucial role in the molecular mechanisms of vasodilation, blood coagulation, and fibrinolysis (Figure 1). The cascade is prompted by the activation of factor XII (Hageman factor) into factor XIIa (activated factor XII), which can be triggered by trauma,[18] microbial infections, or estrogen-containing medications, although activation can also occur with no identifiable clinical triggers. Factor XIIa converts prekallikrein to plasma kallikrein, which cleaves high–molecular weight kininogen (HMWK) to produce bradykinin.[18] Prekallikrein circulates as a bimolecular complex bound to HMWK.[26] Factor XII possesses a trace of intrinsic activity[27] and becomes a substrate upon binding to macromolecular surfaces. Full activation requires enzymatic cleavage through two steps: (1) autoactivation[28] and (2) the rapid activation of factor XII by kallikrein, creating a positive feedback loop.[18,29,30] C1INH inhibits both plasma kallikrein and factor XIIa enzymatic activity.[30,31] When functional levels of C1INH are below 30% of normal physiologic levels, typical in type I and II HAE, the insufficient inhibition of bradykinin-forming enzymes results in bradykinin overproduction. The B2 receptor is activated by brandykinin[32,33] and is thought to cause HAE attacks[18] by triggering vasodilation, increasing vascular permeability and smooth muscle contractions.[32]

The B1 receptor, which is activated by des-arginine9 bradykinin, has a role in vascular permeability and is present when induced by inflammatory cytokines.[34,35] Carboxypeptidases M (endothelial cell surface) and N (plasma) cleave the C-terminal arginine on bradykinin to generate des-arginine9 bradykinin, directly enhancing B1 receptor signaling. When upregulated, the B1 receptor may increase swelling during stress or trauma or after an infection, as supported by *ex vivo* studies.[35] The discovery of the role of bradykinin in the pathophysiology of HAE has led to the search for medications to inhibit the kallikrein-kinin pathway.[33]

Overview of HAE treatment

Hereditary angioedema treatment encompasses on-demand therapies (acute attacks) and prophylaxis. To date, clinical trials have focused on HAE-C1INH; however, clinical experience, open-label studies, and case reports have demonstrated that many treatments designed for patients with HAE-C1INH are also effective for patients with HAE-nl-C1INH.[31]

The goal of on-demand treatments is to prevent asphyxiation and decrease other symptoms associated with an acute attack, including abdominal pain, and peripheral swelling.[13] Rapid treatment with on-demand therapies also substantially shortens the duration of the attack; examples include plasma-derived (pd) or recombinant C1INH (to inhibit the cleavage of HMWK[31]), ecallantide (specifically to inhibit plasma kallikrein), and icatibant (a bradykinin B2 receptor antagonist).[13,23,36] Hereditary angioedema guidelines recommend that attacks be treated with on-demand medications early, regardless of the swelling location, and that all patients have ready access to at least two doses of acute therapy.[4,13,37] Airway HAE attacks can be life-threatening; therefore, patients must have access to acute, self-administered treatment, reducing treatment delays. Self-administration is crucial to control HAE symptoms and can improve QoL by increasing patient independence, reducing health care visits and time away from work.[2,38,39]

Prophylactic treatments are used to prevent and lessen the severity of HAE attacks and include long-term and short-term options (before known triggers, including surgery).[4] Long-term prophylactic treatment should be considered for all patients with HAE, assessing factors such as the frequency of attacks, administration route preferences, QoL, availability of health care resources, failure to achieve sufficient control through on-demand therapies, and importantly, the patient's interest in starting prophylaxis.[4,13] Plasma-derived-C1INH concentrate (intravenous or subcutaneous administration every 3-4 days) and lanadelumab (subcutaneous administration), a plasma kallikrein inhibitor, are recommended as first-line HAE-C1INH prophylactic treatments.[4,13] The most common side effect of pd-C1INH concentrate and lanadelumab is injection-site reactions.[40,41] Thromboembolic events are rare with pd-C1INH and typically occur in patients with existing risk factors or indwelling ports.[13] Preceding the availability of pd-C1INH and lanadelumab, long-term oral androgen therapy and antifibrinolytics were common preventative treatments; however, their potential for adverse side effects and limited efficacy led to high discontinuation rates.[42-44] They should be considered for use only as a last resort.[4]

Over the past decade, the HAE armamentarium has expanded to include several safe and effective therapies including some directly targeting plasma kallikrein.[4] These kallikrein inhibitors[4] work by binding to plasma kallikrein and blocking its binding site, preventing cleavage of HMWK and subsequent generation of bradykinin (Figure 1).[45-48] There has been increased interest in developing these targeted therapies. Two kallikrein inhibitors were approved in the past 3 years and several new kallikrein inhibitors were assessed in clinical trials.[49]

OVERVIEW OF KALLIKREIN INHIBITORS

Acute therapy

Ecallantide. The first selective kallikrein inhibitor approved in the United States was the subcutaneous, reversible inhibitor of plasma kallikrein, KALBITOR (ecallantide),[45] a recombinant

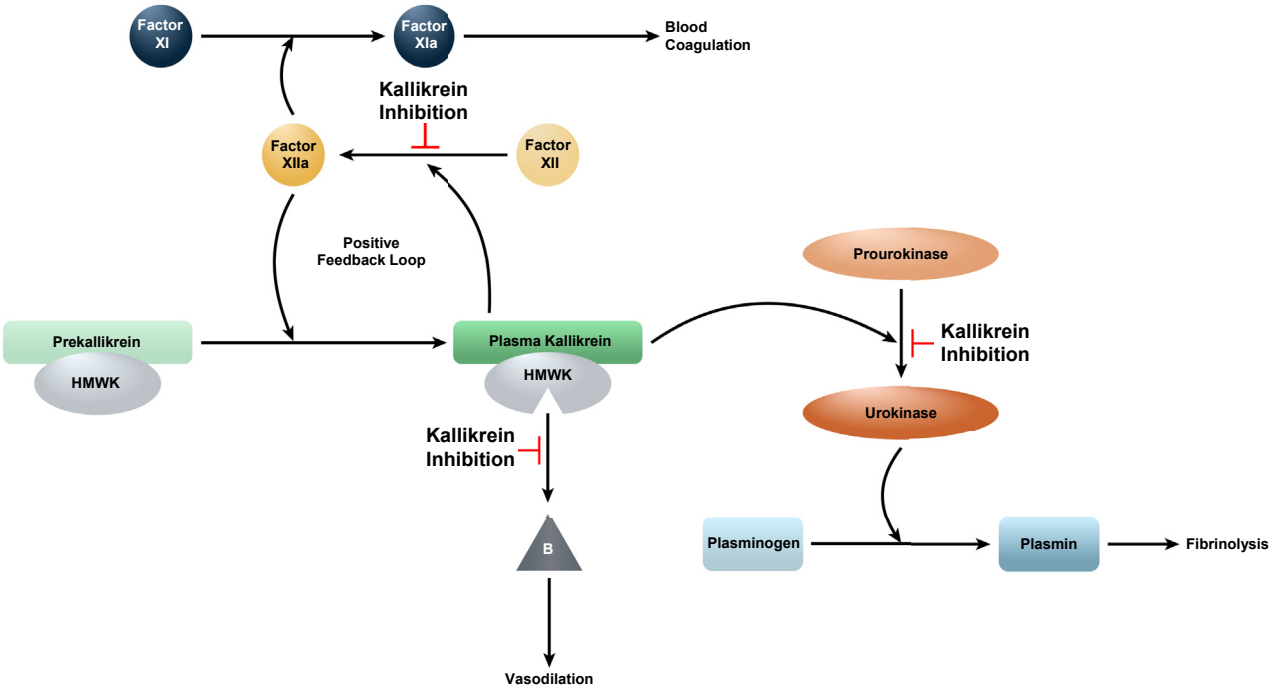

FIGURE 1. Kallikrein function and inhibition. The physiologic role of plasma kallikrein in vasodilation, fibrinolysis, and blood coagulation processes, and pathways blocked by plasma kallikrein's targeted inhibition. *B*, bradykinin; *HMWK*, high–molecular weight kininogen.

protein produced by *Pichia pastoris* yeast.[33,50,51] Ecallantide (DX-88) binds directly to plasma kallikrein to prevent cleavage to HMWK and the generation of bradykinin.[52] Preclinical studies in C1INH-deficient murine models demonstrated that injection with pd-C1INH or ecallantide improved vascular permeability to that of the wild type within 10 minutes, as determined by injection of Evan's Blue dye,[52] suggesting that administration of C1INH and inhibition of plasma kallikrein prevented bradykinin-induced vascular leaks.[52]

The approval of ecallantide in 2009 for on-demand treatment of patients with HAE was based on two randomized, double-blind, placebo-controlled phase 3 studies (EDEMA3 and EDEMA4) in patients aged 12 years and older with HAE-C1INH.[33,45,50,53,54] In EDEMA3 (n = 72), those receiving ecallantide reported a significantly improved ($P = .004$) mean treatment outcome score (a composite, patient-reported outcome measure based on the site[s] of symptoms, symptom severity at baseline, and treatment response) versus placebo.[50] Of patients receiving ecallantide, 50% showed significant improvement in overall response (patients reporting symptom improvements for at least 45 minutes within 4 hours after receiving the study drug) versus 33% of those receiving placebo.[50] In EDEMA4 (n = 96), greater symptom improvement was observed in patients receiving ecallantide versus placebo (−0.8 vs −0.4; $P = .01$), and more patients responded to ecallantide treatment than placebo (44% vs 21%; $P = .02$).[54]

The safety profile of ecallantide was found to be similar to that of placebo with the exception of a low risk for anaphylaxis with subcutaneous dosing.[45,55] A retrospective review of clinical study data found that 3.5% of patients who received subcutaneous ecallantide (eight of 230) experienced hypersensitivity reactions within 1 hour of exposure; this met National Institute of Allergy and Infectious Disease criteria for anaphylaxis.[55] No patient experienced a reaction upon the first exposure to ecallantide, and clinical features of the anaphylactic episodes suggest that they were type I (drug) hypersensitivity reactions.[55] All eight patients survived the reactions, which were treated with standard management of type I hypersensitivity reactions.[55] Because of this potential for anaphylactic reactions, ecallantide has a black box warning and must be administered by a health care professional.[45,55] Anaphylactic reactions appear to be specific to ecallantide and to date have not been reported with other kallikrein inhibitors.[47,56]

Prophylactic therapy

Lanadelumab. The US Food and Drug Administration (FDA) approved the first prophylactic kallikrein inhibitor, TAKHZYRO[47] (lanadelumab) in 2018 for patients aged 12 years and older with HAE. Lanadelumab (DX-2930) is a human IgG1 monoclonal antibody plasma kallikrein antagonist.[41,47,57] It is approved at a subcutaneously injected dose of 300 mg every 2 to 4 weeks.[47] Patients without breakthrough HAE attacks after 6 months can lengthen the interval to every 4 weeks.[47] Similar to ecallantide, lanadelumab was discovered using antibody phage technology.[58] In preclinical studies, lanadelumab was shown to be highly selective for plasma kallikrein and effectively reduced carrageenan-edema in rats (carrageenan is a commonly used phlogistic agent[59]).[58,60] It has a half-life of 12 days in primates, and subcutaneous administration led to a bioavailability of 66%.[58,60,61] Lanadelumab binds to and blocks the active site of kallikrein, preventing the kallikrein-modulated production of bradykinin.[58,60] Phase 1 studies demonstrated that administration significantly prevented the cleavage of HMWK as a direct result of kallikrein

activity and limited kallikrein activation of factor XII, the rate-limiting step for bradykinin formation.[61]

A phase 3, randomized, double-blind, placebo-controlled trial (NCT02586805) evaluated the efficacy and safety of lanadelumab in 125 patients aged 12 years and older with HAE-C1INH.[62] Patients were randomly assigned 2:1 to receive lanadelumab (150 mg every 4 weeks, 300 mg every 4 weeks, or 300 mg every 2 weeks) or placebo for a total of 26 weeks.[62] Treatment with 300 mg lanadelumab every 2 or 4 weeks significantly reduced the number of attacks (mean number of attacks per month: 0.26 (every 2 weeks), 0.53 (every 4 weeks) vs 1.97; $P < .001$).[62] The number of attacks requiring acute treatment was significantly reduced compared with placebo (0.21, 0.42 vs 1.64; $P < .001$). The rate of moderate to severe attacks (0.2, 0.32 vs 1.22; $P < .001$) and the number of attacks during treatment days 14 to 182 were also reduced with lanadelumab (0.22, 0.49 vs 1.99; $P < .001$).[62]

Common adverse events (AEs) included injection-site pain (42.9%), viral upper respiratory tract infection (23.8%), headache (20.2%), injection-site erythema (9.5%), injection-site bruising (7.1%), and dizziness (6.0%).[62] A long-term, open-label safety study (NCT02741596) demonstrated that patients receiving lanadelumab achieved the minimal clinically important difference (−6) in AE-QoL total score.[63]

Emerging therapies targeting plasma kallikrein

One newly approved molecule and several pipeline molecules targeting plasma kallikrein are under development for the acute treatment and long-term prophylaxis of HAE.[49] Many of these new therapies are administered orally.[49] In the 2017 US FDA Patient-Focused Drug Development meeting of 162 patients with HAE, the administration route was the most frequently chosen factor driving treatment preference, in which oral medications were preferred over subcutaneous ones.[64] This is further supported by a 2018 survey in which HAE patients preferred oral medications.[65] Whereas lanadelumab and ecallantide require patient education upon administration, oral medications require no training; therefore, they may provide increased flexibility and ease in medication administration.

Newly approved therapies

Berotralstat. Berotralstat (BCX7353) was approved by the FDA in December 2020 as the first orally administered selective inhibitor of plasma kallikrein to prevent HAE attacks.[56] The recommended dosage is one capsule (150 mg) per day with food.[56] It has a median half-life of 93 hours and reaches steady-state levels in 6 to 12 days.[56]

APeX2 (NCT03485911), a phase 3 study of 121 patients with HAE-C1INH, demonstrated significant reductions in HAE attack rates compared with placebo.[66] The rate of HAE attacks over 24 weeks was significantly lower in both berotralstat treatment groups (110 mg: 1.65 attacks/month, n = 41; and 150 mg: 1.31 attacks/month, n = 40) compared with placebo (2.35 attacks/month, n = 40; $P < .001$).[66] Patients treated with 150 mg berotralstat also experienced a significant reduction in the frequency of on-demand treatment compared with placebo (110 mg: 1.29 attacks/month, $P = .015$; and 150 mg: 1.04 attacks/month, $P < .001$; vs placebo: 2.05 attacks/month).[66] Moreover, 50% (20 of 40) experienced a 70% or greater reduction from baseline in HAE attack rate at 24 weeks, compared with 15% (six of 40) receiving placebo ($P = .002$).[66] Patients experienced attack reductions in the first month of 150 mg berotralstat, which were sustained over the 6-month treatment period. The HAE attack rate was also significantly reduced in the berotralstat treatment groups for those with two or more attacks per month at baseline (110 mg: 1.99, $P = .035$; and 150 mg: 1.76, $P = .005$; vs placebo: 2.92).[66]

APeX-2 demonstrated that long-term use of berotralstat was generally well-tolerated. Of patients treated with 110 and 150 mg berotralstat, 83% (34 of 41) and 85% (34 of 40), respectively, experienced one or more treatment-emergent AE (TEAE) over 24 weeks, compared with 77% receiving placebo (30 of 39).[66] Drug-related TEAEs occurred in 41.5%, 37.5%, and 33.3% of patients receiving 110 mg, 150 mg, and placebo, respectively.[67] The most common TEAEs reported with berotralstat treatment in the first 24 weeks were abdominal pain, vomiting, diarrhea, and back pain.[66] No serious TEAEs were deemed to be related to the study drug by the investigators.[66]

In an interim analysis of an ongoing open-label study of 110 or 150 mg berotralstat (APeX-S, NCT03472040), patients with HAE completing 48 weeks of dosing experienced a median (range) attack rate of 0.0 (0.0,4.0) per month by month 12 of treatment for both dose groups, and reported improved QoL scores.[68]

Investigational therapies

Prophylaxis

ATN-249. ATN-249 (Attune Pharmaceuticals, New York, NY) is an orally administered plasma kallikrein inhibitor under investigation for prophylactic HAE-C1INH treatment.[69] Preclinical, *ex vivo* studies demonstrated that ATN-249 has a selectivity of greater than 2,000-fold in normal human plasma to inhibit plasma kallikrein compared with other closely related serine proteases (eg, thrombin, factor Xa, factor VIIa, and tissue plasminogen activator).[69] Compared with pd-C1INH (Cinryze - Takeda Pharmaceutical Company, Cambridge, MA), a nonspecific kallikrein inhibitor, ATN-249 had greater than 10-fold higher inhibition of plasma kallikrein and contact activation.[69] A dose of 15 mg/mL administered to primates provided 24-hour exposure (C_{24}) 30-fold greater than half maximal effective concentration, suggesting the potential for once-daily dosing.[69] A phase 1, randomized, double-blind, placebo-controlled, single-ascending dose study of ATN-249 (50-800 mg) (ACTRN12618000430235) was conducted with 48 healthy male participants.[70] Dose-dependent inhibition of *ex vivo* triggered plasma kallikrein activity and decreased cleaved HMWK generation were detected 2 hours after administration.[71] ATN-249 was also well-tolerated at the highest dose. All AEs were mild and no dose-limiting toxicity was noted.[72] The authors commented that *in vivo* HAE triggers might be milder than those *ex vivo*; therefore, the therapeutic effect may be larger in patients with HAE.[69]

Acute therapies

KVD900. KVD900 (KalVista Pharmaceuticals, Cambridge, MA) is an oral, small-molecule, selective inhibitor of plasma kallikrein under investigation as on-demand treatment.[73-75] A phase 1, single-administration, dose-escalation study (5 to 600 mg) demonstrated dose-dependent inhibition of *ex vivo* dextral stimulation of plasma kallikrein. At the highest dose of 600 mg, the drug achieved sufficient concentrations less than 20 minutes after administration and maintained greater than 95% inhibition of plasma kallikrein for 8 hours and prevented HMWK cleavage

for 12 hours.[76] KVD900 also inhibited the generation of factor XIIa and the activation of plasma prekallikrein, blocking contact system activation for up to 6 hours.[76]

Results from a phase 2, placebo-controlled, crossover study (NCT04208412) evaluating the efficacy and safety of KVD900 in 53 patients with type I or II HAE were recently reported.[77] The primary end point of the study, time to conventional attack treatment (rescue) use within 12 hours, was significantly reduced by a single dose of KDV900 compared with placebo (15.1% vs 30.2%, respectively; $P = .001$). In addition, KVD900 reduced the time to symptom relief compared with placebo (1.6 vs 9 hours, respectively; $P < .0001$).[77] Phase 3 trial initiation was expected in 2021.[77]

KVD824. KalVista is also developing an oral plasma kallikrein inhibitor, KVD824, for prophylactic use with twice-daily dosing.[78] Over 100 subjects were exposed to KVD824 in safety studies, AE rates were similar between KVD824 and placebo arms, and no serious AEs were reported.[78] A phase 2 study to investigate its efficacy as a prophylactic treatment for patients with HAE was expected to begin in the second half of 2021.[78]

IONIS-PKK-L$_{Rx}$. IONIS-PKK-L$_{Rx}$ is a ligand-conjugated investigational antisense oligonucleotide targeted at prekallikrein in the liver.[79] It is delivered subcutaneously for long-term prophylaxis and has demonstrated tolerability in a phase 1 safety study in healthy participants.[79] IONIS-PKK-L$_{Rx}$ demonstrated a reduction in HAE attack rates in a compassionate-use pilot study with two patients who had severe bradykinin-mediated angioedema.[79] It is currently being investigated in a randomized, double-blind, placebo-controlled phase 2 clinical trial for patients with HAE (NCT04307381).

CONCLUSION

Hereditary angioedema treatment options have significantly expanded in the past few years from poorly tolerated androgens to intravenous and subcutaneous C1INH, and more recently with subcutaneous and oral plasma kallikrein inhibitors. Approved plasma kallikrein inhibitors have evolved, giving patients more options to avoid or minimize HAE symptoms. The development of newer, more easily administered plasma kallikrein inhibitors has simplified treatment for patients and consequently increased independence and reduced treatment burden, which may translate to improved QoL.[80,81] Although beneficial, more medication options have increased the complexity of care; therefore, shared decision-making is essential when determining a treatment plan for patients with HAE. Shared decision-making should incorporate a physician's medical expertise with a patient's care goals to develop a personalized management strategy.[82,83] This collaboration can improve medication adherence, overall health outcomes, and patient satisfaction.[83]

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Update

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Corrections

With regard to the article in the March 2022 issue entitled "Specific Targeting of Plasma Kallikrein for Treatment of Hereditary Angioedema: A Revolutionary Decade" (J Allergy Clin Immunol Pract 2022;10(3):716-22), the authors have amended their Acknowledgments section. It now reads as follows: "Writing and editorial support were provided by Dorothy Keine, PhD, of 3Prime Medical, and Ashly Pavlovsky, PhD, of Porterhouse Medical Group." The authors regret the error.

With regard to the article in the May 2022 issue entitled "Global Variability in Administrative Approval Prescription Criteria for Biologic Therapy in Severe Asthma" (J Allergy Clin Immunol Pract 2022;10(5):1202-1216.e23), one of the authors' name was listed incorrectly. "Daniel J. Jackson, MBBS, MRCP (UK), PhD" should be "David J. Jackson, MBBS, MRCP (UK), PhD" The online posting of the article has been updated with the correct name. The publisher and authors regret the error.