Management of Hereditary Angioedema in Childhood

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Background: Hereditary angioedema (HAE) is a rare disease characterized by recurrent, self-limiting attacks of subcutaneous and submucosal edema. Though a majority of patients will experience symptom onset before 20 years of age, there is a paucity of published literature regarding the management of HAE in children and adolescents.
Methods: A comprehensive literature review regarding the management of pediatric HAE due to C1-esterase inhibitor deficiency (C1 INH) was performed.
Results: A collection of case reports and case series suggest antifibrinolytics and attenuated androgens at low dose are safe and effective options for short- and long-term prophylaxis in pediatric HAE. Plasma-derived C1 INH preparations are available for both on-demand and prophylactic therapy in the United States, and post-hoc analyses of the pediatric patients enrolled in the larger clinical trials support their use in pediatric HAE. Ecallantide and icatibant are kinin-pathway modulators, but only ecallantide is currently approved for use in children 12 years of age and older in the United States. There was no available literature regarding the use of icatibant in pediatric HAE, but ecallantide's efficacy and tolerability were demonstrated in a post-hoc analysis of pediatric patients that participated in four larger, prospective studies.
Conclusions: Within the limits of the present literature review, the currently available and approved therapies used in the treatment of adults with HAE also appear safe and effective for use in children and adolescents at appropriate doses. Options available in the United States include plasma-derived C1-INH, attenuated androgens, and antifibrinolytics for prophylactic prevention and plasma-derived C1 INH and ecallantide for on-demand, acute therapy.

Introduction

HEREDITARY ANGIOEDEMA (HAE) is a rare disease characterized by recurrent episodes of subcutaneous swelling of the skin and submucosal swelling of the gastrointestinal tract or upper airway.[1,2] The swelling is non-pitting and nonpruritic, and occurs without urticaria. Types I and II HAE are due to mutations within the C1-esterase inhibitor (C1 INH) gene and are typically inherited as an autosomal dominant trait, though 25% of cases arise from de novo mutations.[3,4] Type I HAE accounts for 85% of cases and is characterized by low plasma levels of C1 INH. Type II HAE is characterized by normal to elevated plasma levels of a dysfunctional C1 INH and accounts for the remaining 15% of cases.[4] Acquired forms of angioedema associated with C1 INH deficiency and a form of HAE associated with normal C1 INH protein level and function have been described, but are rare in children and not the focus of this review.
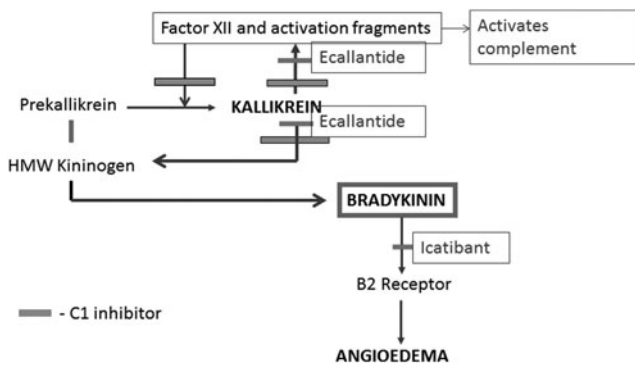
C1 INH protein was named for its ability to regulate the activity of the complement protein C1, but it has since been found to act as a regulator or inhibitor of the clotting, fibrinolytic, and kinin-generating systems in plasma.[5]

The failure of C1 INH to regulate the kinin-generating system adequately is considered the central pathophysiologic mechanism by which C1 INH deficiency results in angioedema.[6] In the absence of C1 INH, activation of kallikrein by Factor XII, and possibly other factors, is unregulated. Unregulated kallikrein activation then results in kallikrein-induced cleavage of high molecular weight kininogen and the formation of the highly potent vasodilator bradykinin (Fig. 1). Bradykinin is the primary mediator of angioedema and acts on bradykinin B2 receptors to enhance vascular permeability.[7,8]

The estimated prevalence of HAE is 1 in 50,000, and there are no known differences in prevalence among ethnic groups or gender.[4] The age of onset is variable, but disease

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FIG. 1. Schematic of pathways of bradykinin generation showing points of pathway inhibition by new medications.

manifestations typically begin between 5 and 11 years of age.[9] A large series of HAE patients from Germany showed a mean age of onset at 11.2 years, with almost 90% of patients experiencing onset of symptoms by the age of 20 years.[10] In an additional series of HAE patients, 50% of patients had their first attacks before the age of 10 years and 85% before the age of 20 years.[11] Symptom severity and attack frequency increase between 3 and 6 years of age and again around the onset of puberty.[9] There is suggestion that the earlier the onset of symptoms, the more severe the course of HAE.[9,10]

HAE attacks are typically self-limited, with an average duration of 2–5 days. Subcutaneous attacks localized to the extremities and recurrent colicky abdominal pain are the most common manifestations in children.[9] Attacks are often preceded by a prodromal phase, and the characteristic prodromal erythema marginatum is estimated to occur in 30–50% of patients.[12,13] Upper airway edema is life-threatening, potentially fatal, and has been described in a child as young as 3 years of age.[9,14] Possible attack triggers are numerous and include infection, stress, and mechanical trauma.[9] Mild dental manipulation has also been observed to precipitate an HAE attack.[15] Many attacks, however, occur spontaneously and with no known cause. HAE causes a significant decrease in quality of life and has been shown to impact education, career, and work productivity.[16]

Treatment options for HAE may be divided into management of acute attacks, short-term prophylaxis, and long-term prophylaxis. Both acute and prophylactic treatment of HAE has been revolutionized in the past decade, with the addition of new, effective agents added to the armamentarium for therapy.[17,18] Though HAE often presents in childhood or adolescence, published literature focused on the treatment of HAE in pediatric patients is scarce. Comprehensive consensus recommendations for HAE disease management were issued in 2010, but the guidelines fail to address pediatric HAE specifically with any robust, evidence-based support.[15] The purpose of this article is to review the recent and relevant literature to provide guidance and support the principles of treatment in pediatric HAE in the United States.

Methods

A comprehensive literature search was conducted using the National Library of Medicine (Pubmed MEDLINE). Using appropriate medical subject headings and keywords,

articles related to the treatment of children and/or adolescents with HAE due to C1 INH deficiency were sought. Only articles written in English were included in this review.

Results

Management of HAE is traditionally classified into rescue treatment of acute attacks, short-term prophylaxis, and long-term prophylaxis.[19] Effective prophylactic therapy, both short- and long-term, has long been provided by attenuated androgens and antifibrinolytics, but their use is limited by untoward side effects.[17,18] The introduction of new and effective therapies for patients with HAE has revolutionized the treatment landscape. Though plasma-derived C1 INH therapy for HAE has been available abroad for more than three decades, these drugs were only imported into the United States and approved by the Food and Drug Administration (FDA) within the last 5–6 years. Plasma-derived C1 INH is currently approved for both prophylactic and on-demand therapy in HAE.[17,18] A recombinant form of human C1 INH (Ruconest; Salix Pharmaceuticals, Raleigh, NC) has only recently obtained FDA approval in acute treatment of HAE in adults and adolescents. Ecallantide and icatibant are both kinin-pathway modulators, but only ecallantide is currently FDA approved for the acute treatment of HAE attacks in children 12 years of age and older.[18] Each of these medications is discussed in further detail, supplemented by a review of available and relevant literature regarding their use in pediatric HAE.

Antifibrinolytic agents

The precise mechanism of action of antifibrinolytic agents in treated HAE is unclear. Among the antifibrinolytics, tranexamic acid (TXA) is preferred over epsilon aminocaproic acid (EACA) for prophylaxis, but there are no head-to-head drug comparisons.[9] In an early double-blinded, crossover trial, treatment with EACA resulted in a reduction, but not complete resolution, of attacks in seven children with HAE.[20] Children younger and older than 11 years of age tolerated 3 g and 6 g respectively of EACA per day without side effects. At larger doses of >12 g/day, however, the children experienced nausea, diarrhea, dizziness, and myalgias, all well-known side effects of EACA. Moreover, in the experience of one of the authors, long-term use of EACA in childhood is associated with severe fatigue and poor school performance. In another cohort, long-term prophylaxis with either EACA or TXA was initiated in 11 children with HAE, and three achieved complete remission on 1–2 g/day of TXA.[21] Antifibrinolytic therapy, however, was ineffective in the remaining eight children. For short-term or perioperative prophylaxis in children, TXA 500 mg orally four times daily for 5 days before and after surgery has been recommended.[22] It is also reasonable to consider plasma-derived C1 INH therapy alone or one of the newer agents shown to be effective for acute HAE attacks as better choices. Evidence suggests, however, that short-term prophylaxis is less often required in children, except when undergoing procedures involving the head or neck region.[15]

Androgens

The efficacy of attenuated androgens in HAE is partially explained by a rise in plasma levels of C1 INH and possibly

accelerated catabolism of bradykinin.[23] There is a collection of cases and case series suggesting attenuated androgens are both effective and tolerable in children with HAE.[24–28] Danazol 100–200 mg/day resulted in complete elimination of more severe attacks in eight children with HAE who failed previous therapy with TXA.[21] In addition, remission was maintained, despite tapering the interval to alternate or third daily dosing. Attenuated androgens are often used for short-term prophylaxis, with recommended doses of 2.5–10 mg/kg/day in divided doses and to a maximum of 600 mg/day (22, 23). Therapy is typically started 5 days prior and for 2–5 days following the intervention. Since attenuated androgens can accelerate epiphyseal closure with attendant growth retardation, their use should be carefully monitored.

Plasma-derived C1-INH concentrate

Purified C1 INH was first used as treatment of HAE in 1980, and its use in children was reported as early as 1989.[29,30] Cinryze (ViroPharma, Exton, PA) and Berinert (CSL-Behring, King of Prussia, PA) are the only preparations of plasma-derived C1 INH available in the United States, and are currently only approved for use in adolescent and adult patients with HAE. International consensus reports indicate plasma-derived C1 INH is suitable for treatment of pediatric HAE.[15] In addition, the efficacy and tolerability of plasma-derived C1 INH in pediatric HAE has been the focus of and reported in several publications.[21,30–34] Home therapy with plasma-derived C1 INH may even be a safe and effective treatment option in pediatric patients, given appropriately instructed and educated families.[31,32] Median times from attack onset to start of treatment and from start of treatment to initial symptom relief were both significantly shorter with home therapy compared to physician-based therapy.[32]

The International Multicenter Prospective Angioedema C1-INH Trial 1 (I.M.P.A.C.T.) was a randomized, double-blind, and placebo-controlled trial of Berinert for the treatment of facial and abdominal attacks in adolescent and adult patients with HAE due to C1 INH deficiency.[35] I.M.P.A.C.T. 2 was an open-label, uncontrolled, extension study of I.M.P.A.C.T. 1 and investigated the efficacy and tolerability of Berinert 20 U/kg for acute HAE attacks involving any location.[36] For both trials, the primary endpoints were the times from start of treatment to initial symptom relief and to complete relief of all symptoms.

A post-hoc analysis of pediatric patients < 18 years of age involved in the I.M.P.A.C.T. 1 and 2 trials was recently performed to evaluate the safety and efficacy of Berinert in this patient population.[37] Seven patients from I.M.P.A.C.T. 1 with an age range of 10–17 years were included in the analysis. Median time to onset relief was 0.42 h and to complete resolution was 8.08 h, and no placebo analysis was performed. Nine patients from I.M.P.A.C.T. 2 with an age range of 10–17 years met study entry criteria. A total of 115 attacks were included, and median time to onset relief was 0.49 h and to complete relief was 14.1 h. Between the two studies, only four treatment-emergent adverse events were identified, and only two were ultimately considered related to study medication. Though vigorous, definitive conclusions cannot be made without placebo comparison and larger sample sizes, the post-hoc analysis results show pediatric patients respond to and overall tolerate C1 INH therapy for acute HAE attacks.

Cinryze was approved in the United States for routine prophylaxis in adolescent and adult patients with HAE based on the results from pivotal prospective, randomized, and placebo-controlled studies.[38] Open-label extension studies of Cinryze for on-demand and prophylactic HAE therapy were later conducted and only included patients who completed the previous placebo-controlled studies.[39,40] In the acute treatment trials, the primary endpoint was time to unequivocal relief, defined as three consecutive reports of resolved or improved symptoms.[38,39] In the prophylaxis trials, the number, duration, and severity of HAE attacks during were assessed, and the primary end point was the number of angioedema attacks per treatment period.[38,40]

Data from the two placebo-controlled studies and two open-label extension studies were later used for a post-hoc analysis of the participating pediatric patients < 18 years of age.[41] Forty-six children and adolescents with an age range of 2–17 years were included in the analysis. In the placebo-controlled, acute-attack treatment study, 71% of children who received Cinryze for treatment of an acute attack achieved unequivocal relief within 4 h, compared to 40% receiving placebo. For those children who achieved unequivocal relief, median time to the start of unequivocal relief was 0.5 h with Cinryze and 2 h with placebo. In the open-label, acute-attack treatment study, unequivocal relief of the defining symptom started within 1 h after the initial Cinryze dose in 79% of attacks and within 4 h in 89% of attacks. Results from the placebo-controlled and open-label studies for prophylaxis showed that most children who received prophylaxis therapy with Cinryze had a reduced attack rate. Specifically, children had a reduction in the mean number of attacks (over 12 weeks) from 13.0 to 7.0 in the placebo-controlled trial, and a reduction in median monthly attack rate from 3.0 to 0.39 in the open-label extension study. Taken all together, these results offer strong evidence supporting the clinical use of Cinryze in the management of children with HAE.

All plasma products have risk of infection, but the risk is considered minor for the currently available C1 INH products because they have been used abroad for decades and no infection has been observed.[17] In addition, there was no evidence of viral transmission in the post-hoc analyses of the pediatric patients who participated in the larger clinical trials for both Berinert and Cinryze.[37,41]

Though the referenced case series and post-hoc analyses provide a general sense that purified C1 inhibitor products are effective and overall well-tolerated in pediatric patients with HAE, it is worthwhile mentioning that a majority of pediatric patients included in the post-hoc analyses were adolescents. In addition, the FDA-approved patient package inserts for Berinert and Cynrize note that their safety and effectiveness have not yet been established in children.[42,43] Studies are ongoing, however, to determine better the efficacy and safety of both plasma-derived and recombinant C1 inhibitor in younger pediatric patients with HAE.[44–46]

Ecallantide

Ecallantide (Kalbitor; Dyax Corp., Burlington, MA) is a plasma kallikrein inhibitor, currently indicated for acute treatment of HAE attacks in patients aged 12 years and older. A recent analysis suggested that ecallantide is effective for the treatment of HAE attacks in pediatric patients

and has an acceptable safety profile.[46] Data for patients aged 9–17 years treated subcutaneously with either ecallantide 30 mg or placebo were pooled from four studies: two double-blind, placebo-controlled trials and two open-label studies. Efficacy endpoints included the mean symptom complex severity (MSCS) score and the treatment outcome score (TOS). The MSCS score is an arithmetic mean of severity across all affected locations, and a minimum change of -0.30 points was determined to be clinically meaningful during the validation process.[47] The TOS is a composite measure of response to treatment over time based on a scale of 100 (significant improvement) to -100 (significant worsening). A minimum change in the TOS by 30 points is considered clinically important.

Across the studies, 29 patients aged 9–17 years were treated with either 30 mg subcutaneous ecallantide or placebo. At 4 h after treatment, patients who received ecallantide showed substantial improvement, with a mean decline in MSCS score by 1.4 points compared to 0.9 points in placebo-treated patients. Ecallantide-treated patients achieved the clinically important change of 30 points in TOS by 1 h post-treatment versus 4 h in patients treated with placebo. The cohort only experienced one treatment-emergent adverse event—staphylococcal cellulitis, which was ultimately judged to be unrelated to treatment. Though ecallantide has been associated with hypersensitivity reactions, none was reported in this patient population. In this analysis, ecallantide substantially and rapidly decreased symptom burden and appears to be a potentially effective and safe treatment option for children with HAE.

Icatibant

Icatibant (Firazyr; Shire, Lexington, MA) is a bradykinin B2 receptor antagonist and is currently only approved for treatment of acute HAE attacks in patients 18 years of age and older. A pharmacokinetic, tolerability, and safety study of icatibant in pediatric HAE patients <18 years of age is currently ongoing.[48] Our literature search otherwise did not yield any published works regarding the use of icatibant in the treatment of pediatric HAE. The current dosing recommendation is 30 mg subcutaneously at intervals of at least 6 h, with a maximum of three injections within 24 hours.[23]

Conclusions

HAE due to C1 INH deficiency is a rare disorder with autosomal dominant inheritance. The disease is characterized by recurrent, self-limited attacks of subcutaneous and submucosal swelling, caused by the unregulated production of the potent vasodilator bradykinin. Though a majority of affected patients will experience symptom onset in childhood or adolescence, there are limited published data to guide the management of pediatric HAE. In addition, several new and effective HAE therapies have added to the collection within the last decade, but robust data are lacking regarding their efficacy and safety in children with HAE. A review of case series and post-hoc analyses of larger trials provides a general sense that the products currently approved for use in adults are also safe and effective for use in pediatric HAE. International consensus recommendations do exist, but there is still an unfulfilled need for large-scale, prospective, and multicenter trials to provide stronger evidence-based support for these guidelines in the management of pediatric HAE.

Author Disclosure Statement

No competing financial interests exist.

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