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Future Therapy for Pediatric Hereditary Angioedema

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Hereditary angioedema (HAE) due to C1-inhibitor (C1-INH) deficiency is characterized by recurrent attacks of swelling with symptoms typically beginning in childhood. The introduction of targeted therapies for prevention and treatment of attacks has been of significant benefit to patients, including children, with HAE. However, the ideal of a safe, convenient therapy that prevents all attacks has not been realized. New approaches including ongoing inhibition of plasma kallikrein, and perhaps activated Factor XII, show promise in further improving the care of patients with HAE.

Introduction

Hereditary angioedema due to a deficiency in the C1-inhibitor (C1-INH-HAE, hereafter referred to simply as HAE) is a rare disease characterized by episodic attacks of submucosal or subcutaneous swelling, most commonly affecting the skin, gastrointestinal tract, and upper airway.[1–3] Attacks typically last 2–4 days, are extremely painful, and can result in substantial disability or, in the case of airway obstruction, death.[4] Type I and II HAE result from decreased levels or function of the protein C1-esterase inhibitor (C1-INH), respectively.[1–3] HAE is inherited in an autosomal dominant manner, and results from insufficient C1-INH activity. Approximately one-fourth of cases represent *de novo* mutations, and are not associated with a positive family history.[5] While C1-INH acts to inhibit a number of proteases, conclusive evidence demonstrates that increased activity of plasma kallikrein is the cause of HAE attacks.[6] Plasma kallikrein catalyzes the cleavage of bradykinin from high molecular weight kininogen. Bradykinin then binds to the bradykinin-2 receptor (B2R) on endothelial cells, increasing vascular permeability and leading to angioedema.[6] The reason that attacks are intermittent and limited in both location and duration is not fully understood.

Swelling can be seen as early as infancy, but attacks typically become more frequent at the time of puberty.[3] In girls, increased endogenous estrogen levels may precipitate this increase, but the reason for increased severity in boys is unclear. The pattern of attack frequency and severity set in adolescence often persists into adulthood. Prompt diagnosis of HAE is important, as a recent study showed a significantly increased risk of asphyxiation from upper airway attacks in patients unaware that they had HAE.[4] Thankfully, deaths among children and adolescents are rare in this population.[4]

Current Treatment of HAE

Until recently, safe, effective therapies for the prevention and treatment of HAE attacks were unavailable in the United States. Long-term prophylaxis was limited to attenuated androgens and antifibrinolytics.[7,8] While effective, the myriad side effects observed with androgens are problematic, particularly for children who are still growing, due to the risk of early cessation of bone growth and, in females, because of androgen's virilizing effect. Antifibrinolytics are of uncertain efficacy and also cause significant side effects in some patients.[9] Attenuated androgens were effective as short-term prophylaxis prior to dental or surgical procedures, and fresh frozen plasma (FFP) was also used in this capacity. Treatment of acute attacks largely focused on pain relief and other supportive measures, although FFP was used by some centers.[10]

The treatment landscape has been altered by the introduction of several safe, effective therapies for HAE. These include purified plasma C1-INH (Cinryze, Shire; Berinert, CSL Behring), Ecallantide (Kalbitor, Dyax), and Icatibant (Firazyr, Shire).

C1-INH purified from donor plasma is available for both prevention (Cinryze) and treatment (Berinert) of attacks, while ecallantide, a potent kallikrein inhibitor, and icatibant, a bradykinin-2-receptor blocker, can be used for treatment of acute attacks. Recombinant C1-INH (rhC1-INH, Rhucin) produced in rabbits is available for treatment of acute attacks in Europe, and was recently approved in the United States. The different therapies for treatment of acute attacks have all demonstrated significant efficacy in clinical trials, with no data available directly comparing their effectiveness.

Unfortunately, access to these new therapies is limited by age. C1-INH for both treatment and prophylaxis along with

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ecallantide are currently FDA approved for treatment of patients aged 12 years and older, while icatibant is only approved for patients aged 18 years and older. For C1-INH, significant data indicate safety and efficacy in children younger than 12 years of age,[3] and this therapy is often used off-label for younger patients. Extending the age indication for these medications so that all patients with HAE, including children, can benefit from these medications is a key objective in improving pediatric HAE care. Trials for C1-INH, rhC1-INH, ecallantide, and icatibant are in planning, are underway, or have been completed. Results of these trials should allow FDA approval of these medications for an expanded age range of patients.

Future Therapies for HAE

While modern, targeted therapies represent an enormous step forward for patients, including children, with HAE, they are far from ideal, even if they were to be approved for all age ranges. Prophylactic therapy with purified C1-INH reduces but does not eliminate attacks, and in most patients it requires twice weekly intravenous (i.v.) dosing.[11,12] C1-INH has also been associated with thrombotic events.[13] While the relevance of this to the doses used in patients with HAE is uncertain, at a minimum it makes use of permanent venous access for infusion problematic. Studies of subcutaneous administration of purified C1-INH, which would obviate this concern and make it more acceptable to patients, are underway. Likewise, acute therapies help reverse attacks but can be inconvenient to access and may require substantial alterations in the pattern of daily living. Further, they can be associated with significant adverse effects. For example, both ecallantide and recombinant C1-INH have been associated with hypersensitivity reactions.

An ideal therapy for HAE would be 100% effective in preventing attacks and easily administered either orally or with infrequent i.v. or subcutaneous dosing. This ideal therapy would also be free from major side effects, including thrombosis, risk of infection, and allergic reaction. While not yet available, several medications in the early stages of development show promise in making substantial progress toward this ideal. Potential therapies meeting some or all of these criteria are discussed below.

Oral Kallikrein Inhibitor

BCX4161 is an orally available plasma kallikrein inhibitor developed and being evaluated for the prevention of HAE attacks by BioCryst Pharmaceuticals. It has been extensively evaluated in preclinical models and in a single phase I trial in healthy volunteers.[14,15]

In vitro data demonstrate that BCX4161 is a potent inhibitor of plasma kallikrein, suggesting it would be effective in preventing HAE attacks.[14] *In vitro* assays using plasma donated from patients with HAE between attacks showed BCX4161 is approximately 15 times more potent than native C1-INH in inhibiting kallikrein activity.[14] BCX4161 was then given to normal adult volunteers (i.e., without HAE) as part of a phase I study.[15] Both single doses and dosing every 8 h for a 1 week period were studied. Patients who received 400 mg of BCX4161 every 8 h showed a trough plasma concentration of 29.6 nm, suggesting that with this dosing regimen, plasma kallikrein activity would be effectively inhibited on an ongoing basis.[15] The measured half-life in normal volunteers was 13 h, so twice daily dosing might be feasible.[15] BCX4161 was well tolerated in this study, with some gastrointestinal symptoms developing in volunteers receiving doses >400 mg. Interestingly, similar symptoms were also seen in patients receiving placebo.[15]

Oral Prophylaxis S1 (Opus-1) is a phase II trial of BCX4161 recently completed in Germany and the United Kingdom.[16,17] This trial compared BCX4161 400 mg three times daily versus placebo in a randomized, double-blind, crossover design. Each of approximately 25 patients received both study drug and placebo with a primary outcome measure of number of acute HAE attacks. Initial results showed a decrease in HAE attacks in treated patients.[16,17]

Anti-Kallikrein Antibody

An alternative strategy to inhibit plasma kallikrein is use of a long-acting antibody. DX-2930 is a fully humanized monoclonal antibody, which binds and inhibits plasma kallikrein, and is under development for prophylaxis of HAE by Dyax.[18,19]

In vitro DX-2930 is a potent inhibitor of plasma kallikrein. In solution, DX-2930-inhibited plasma kallikrein with an IC50 (the concentration of protease required to inhibit 50% of plasma kallikrein activity) roughly 100-fold less than C1-INH, indicating high potency.[18] An alternative assay, the ability to inhibit plasma kallikrein bound to umbilical vein endothelial cells, showed >200-fold increased affinity compared to C1-INH.[18] In a recent phase Ia trial of DX-2930, healthy volunteers received escalating doses of DX-2930 or placebo subcutaneously.[19] At higher doses, plasma levels were judged sufficient to inhibit plasma kallikrein activity. The half-life was 17–20 days, suggesting infrequent administration would be required.[19] The most commonly reported adverse effect was headache, but this was reported equally in volunteers receiving DX-2930 and placebo. Dyax, the manufacturer, is performing a phase Ib study of administration of DX-2930 in patients with HAE.[19,20]

Anti-Factor XIIa Antibody

An alternative approach to preventing bradykinin generation and hence HAE attacks would be the inhibition of activated Factor XII. Factor XII is typically thought to autoactivate to Factor XIIa, which subsequently catalyzes the conversion of prekallikrein to kallikrein. Kallikren can then activate Factor XII leading to a positive feedback loop and ultimately amplifying bradykinin generation.[21,22] While some recent data indicate prekallikrein can be auto-activated to kallikrein or via the activity of other proteases,[23] Factor XIIa remains a potential target to prevent HAE attacks. A monoclonal antibody against Factor XIIa was recently described.[24] Its activity was investigated in a rabbit model of extracorporeal membrane oxygenation (ECMO), a therapeutic maneuver used in severe life-threatening lung injury.[24] The antibody significantly decreased the incidence of thrombosis, a major complication of ECMO, without increasing bleeding, as would be predicted from studies of humans and mice lacking Factor XII activity (see below). The ability of this antibody to prevent kallikrein inhibition and subsequently prevent HAE attacks remains to be established but should be considered. In addition, other Factor XIIa inhibitors have been

developed, but their potential use in HAE would appear to be limited by the need for frequent i.v. or subcutaneous dosing.[25]

Potential Adverse Effects of Kallikrein or Factor XIIa Inhibition

While inhibition of plasma kallikrein represents an attractive target for treatment of HAE, there are little data about the long-term safety of this approach. In healthy humans, bradykinin production occurs at low levels constitutively and increases dramatically under certain conditions.[22] Bradykinin binds to two receptors—B1 and B2—with the B2 receptor being primarily implicated in HAE. B2 receptors are expressed constitutively on the surface of endothelia cells, while B1 receptors are induced by inflammation and injury.[22] *In vitro* and *in vivo* data ascribe a number of activities to bradykinin. These include vasodilation and resultant decrease in blood pressure, as well as anti-proliferative and both antithrombogenic and antifibrinolytic activity.[22] All of these activities can be detrimental or beneficial depending on the context.

Mice deficient in plasma kallikrein are phenotypically normal.[26] They display prolonged activated partial thromboplastin time (aPTT), a marker of blood coagulation, but are not at increased risk of bleeding. In fact, they seem to be protected from both arterial and venous thrombosis, and plasma kallikrein inhibition has been considered as a possible preventive therapy for thrombotic disorders such as myocardial infarction and thrombotic stroke.[26]

Congenital plasma kallikrein inhibition has been identified in humans, where prekallikrein was historically referred to as ''Fletcher factor'' based on the name of the first identified family with the deficiency.[27] The index case was identified due to a prolonged aPTT on routine presurgical screening and, analogous to the mouse, no increased history of bleeding.[27] Characterization of family members showed three siblings with a similar phenotype. Patients with Fletcher factor deficiency appear to be healthy without increased risk of thrombosis or bleeding.[27]

While both mice and humans lacking kallikrein activity are without obvious defects and perhaps even protected from thrombosis, the data available are limited, particularly with respect to humans. While long-tern inhibition of plasma kallikrein should prevent attacks of HAE without serious adverse effects and might even be protective against thrombosis, the safety of such an approach in a large group of patients with HAE remains unproven. Any adverse effects might be significantly more pronounced, with kallikrein inhibitors significantly more potent than native C1-INH. Subtle changes such as increased blood pressure or defective fibrinolysis may be absent in the mouse and not observed in the few prekallikrein-deficient patients. Ecallantide, while well tolerated, is used for treatment of HAE attacks. It has a short half-life and does not cause long-lasting inhibition of plasma kallikrein. The long-term safety of kallikrein inhibition, by either an oral inhibitor or long-acting antibody, can only be established by clinical trials.

Similar concerns apply to ongoing Factor XIIa inhibition. Humans lacking Factor XII (also called Hageman factor) appear normal and have a phenotype similar to those lacking kallikrein: increased aPTT but no increase in clinical bleeding.[27] Recent data on Factor XII–deficient mice also indicate a decreased risk of thrombosis without increase frequency of bleeding.[28] While there have been a number of Factor XII–deficient patients who suffered from thrombosis clinically, recent data indicate protection from thrombosis in patients with a deficiency in Factor XII.[25] Nonetheless, caution is warranted until the safety of Factor XIIa inhibition is demonstrated, particularly in HAE patients for whom long-term treatment would be required.

Summary

The last 6 years have seen dramatic improvement in the treatment options available for patients with HAE in the United States, with approval of targeted therapies for both prevention and treatment of acute attacks. Expanding the indications for these therapies to include children of all ages should allow better care for children with HAE. Meanwhile, the field continues to move rapidly forward. New approaches currently under active investigation include inhibition of plasma kallikrein by both an oral small-molecule antagonist and a long-acting inhibitory antibody. Alternative approaches might include inhibition of Factor XIIa, which is currently being pursued as a therapy for other illnesses caused by thrombosis. These novel therapies should help move the field closer toward the ultimate goal of a therapy that effectively prevents all HAE attacks with minimal inconvenience to patients.

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