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Current and future therapy of hereditary angioedema due to C1 inhibitor deficiency

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Abstract

Hereditary angioedema (HAE) is an autosomal dominant disease characterized by recurrent angioedema episodes of life-threatening angioedema. Attacks of angioedema in HAE patients last 3 or more days, begin during childhood, and continue to occur throughout life. Tragically, patients with HAE continue to die as a direct consequence of the disease. Minimizing the morbidity and mortality associated with HAE requires both effective treatment of acute attacks as well as strategies to prevent HAE attacks. Treatment usually involves a combination of prophylaxis, using androgens or antifibrolytic drugs, and replacement with C'1 esterase inhibitor concentrate for acute attacks and before surgery or other traumatic procedures.This review will recap the past treatment options, review the new current treatment options, and discuss potential future treatment options for patients with HAE.

Introduction

Complement system is classic pathway antigen-antibody complexes activate C1to form protease which cleaves C2, C4 and C3 convertase which cleaves C3 this cascade continue to C9, in order to stop this cascade C1 is inhibited by C1 esterase inhibitor enzyme. deficiency in this enzyme can cause angioedema.(1)

Hereditary angioedema (HAE) is an autosomal dominant disease. caused by C1 esterase inhibitor deficiency. It is characterized by swelling episodes that affect the skin or mucous membranes, gastrointestinal tract and upper airways. Laryngeal edema can be life threatening. Biochemical diagnosis can be established by diminished C4 levels and low C1 inhibitor levels or function. Patients with HAE type I (85%) have reduced antigenic and functional C1 inhibitor levels, whereas patients with HAE type II (15%) show only a reduction in C1 inhibitor function. During the past 2 decades, the new estrogen-dependent inherited angioedema without C1 inhibitor deficiency, also referred to as HAE type III. (1)

Minimizing the morbidity and mortality associated with HAE requires effective treatmen, Treatment goals include preventing the attacks, reducing the frequency, severity, and duration of attacks to normalize the quality of patient’s life.

This report will review both the current and the future therapeutic options for the treatment of HAE. Current treatment of HAE (Danazol as a long-term prophylaxis and

short-term prophylaxis). Future treatment of HAE (Purified C1 inhibitor replacement, Recombinant human C1 inhibitor, Plasma kallikrein inhibition).[1]

Result

Berinert human plasma-derived C1 inhibitor (C1-INH) concentrate, is being investigated in 2 international, multicenter, prospective trials. Experience with this agent in Europe and Canada indicates it is effective and safe. Cinryze is a nanofiltered C1-INH replacement therapy demonstrated to be effective and safe in acute and prophylactic, Recombinant human C1-INH replacement therapy from transgenic rabbits, has been shown to be effective and safe in c1s-inhibitor phase 2 and phase 2/3 studies, with an additional phase 3 study ongoing.

DX-88, a potent and specific inhibitor of plasma kallikrein , achieved all primary and secondary efficacy end points in a placebo-controlled.[2]

Discussion

Treatment recommendation of HAE

Current treatment of HAE:

Attenuated androgens have been used for a long term prophylaxis

Danazol (200mg/day) significantly reduced number of attacks but not all patients respond to androgen treatment and it efficacy can decline after several years of administration. attenuated androgens are the only available effective drugs for oral prophylaxis against angioedema attacks. Side effects of danazol include, weight gain menstrual disorder (four out of five) and virilization in women, hepatotoxicity as well as atherosclerosis, depression and atrial hypertension, and hemorrhagic cystitis in long term use studies found that 30 out of 118 patients discontinued danazol from its side effects. [3]

and its contraindicated in pregnancy, lactation, childhood, prostate cancer, sever heart, liver and renal failure. The short-term prophylactic use of danazol in patients with hereditary angioedema undergoing oral surgery is an effective preventive measure.

Short-term therapy of 96-hr duration with tranexamic acid was prophylactically effective as defined by the absence of attacks of angioedema in 14 patients with hereditary angioedema undergoing 10 dental and 4 general surgical procedures. Eight of the 14 patients had previously undergone dental extractions without

prophylactic therapy with antifibrinolytic agents and each had experienced one or more attacks of angioedema. Seven of these 8 patients had a cumulative experience of 13 episodes of laryngeal edema after dental extractions and the eighth had a bout of cutaneous angioedema. Although the number of dental extractions conducted without prophylactic antifibrinolytic therapy cannot be accurately defined in retrospect, the prominence of laryngeal edema in this circumstance is striking when compared with the absence of attacks in the presence of prophylaxis with tranexamic acid. Methyltestosterone and impeded androgens are now known to be effective prophylaxis for spontaneous and, presumably, postoperative attacks when employed chronically because their administration is associated with correction of the biochemical defect of hereditary angioneurotic edema, but their chronic administration to children and women of childbearing age requires further definition because of their potential pituitary suppressive action. Tranexamic acid prophylaxis makes it possible to offer to untreated patients with hereditary angioneurotic edema dental work and other operative procedures that in the past were withheld or conducted with considerable risk.

Future treatment of HAE:

1. Recombinant human C1 inhibitor (Berinert)

is the only C1 esterase inhibitor (C1-INH) approved for reatment of acute abdominal, facial, laryngeal attacks of (HAE) in adults and pediatrics, the safety and efficacy of BERINERT for prophylactic therapy have not been established. patients for early signs of hypersensitivity reactions (chest tightness, urticaria, wheezing, hypotension, and anaphylactic shock). if hypersensitivity reaction is suspected, Berinert should be immediately discontinue and start an appropriate treatment. Epinephrine should be available for treatment of acute severe hypersensitivity reactions.

Dysgeusia is the most common adverse reaction that have been reported in more than 4% of subjects. Early injection is recommended in acute attacks. Initial improvement usually start 30–60 min following the intravenous injection.

Berinert, Cinryze, and Ruconest are recombinant human C1 inhibitor they are approved for self- administration at home ONLY for intravenous administration. Patients require appropriate training for self-administration where necessary, in the presence of family members. The training is comprehensive and covers information on the basics of anatomy, compliance with hygiene measures, preparing the injection

solution, intravenous injection technique, how to respond in the case of complications or inadequate effects.

2. Bradykinin receptor 2 antagonist (Icatibant) angioedema has different causes and different clinical presentations. types of angioedema may be mediated by bradykinin is one of the new therapies for HAE

it is effective by selectively antagonizing the binding of bradykinin to the bradykinin B2 receptor inhibits bradykinin-induced vasodilation in humans to treat the attacks , and it does not interact with bradykinin B1 receptors or other peptide receptors, studies showed Icatibant is effective and safe in skin swelling and abdominal attacks for HAE compared to tranexamic acid and the symptoms are decreased within 4 hours after administration of Icatibant, Icatibant is also effective in laryngeal edema. Icatibant has been approved for self-injection by patients since 2011. [4]

Plasma kallikrein inhibition

Ecallantide (known as DX-88 previously)

a highly specific recombinant plasma kallikrein inhibitor that stop the production of bradykinin and can be given subcutaneously. This drug has been available in clinical practice since 2009 in the US and it is the only product approved recently by the FDA for all localizations of edematous HAE attacks occurring in patients over 16 years of age. Patients developed antibodies to ecallantide. Anti-ecallantide antibodiesof all classes and of IgE type against host cell proteins did not appear to correlate with the occurrence of adverse events. Overall, 7.4% of patients seroconverted to anti-ecallantide antibodies. The incidence of seroconversion seemed to increase with increasing drug exposure. No information is available on drug interactions, as no relevant studies have been conducted.We describe our institution’s experience in treating an HAE family, affected father with his two affected daughters, with DX-88 in a jointly conducted adult and pediatric hematology clinical trial. EDEMA I is an ascending four dose placebo controlled study to assess the efficacy and tolerability of DX-88 for acute attacks of HAE. Patients presented for treatment within 4 hours of a moderately severe acute attack and were observed for 8 hours. All three presented with abdominal attacks. The first daughter, on Oxandrin prophylaxis, presented with cramping, gnawing abdominal pain, associated nausea and rash. Subjective resolution of nausea, cramping and rash occured within 1 hour of treatment. The abdominal distention had partial resolution with continuing response up to 8

hours.The second daughter had more severe recurrent symptoms associated with her menses. She used imported C1-INH concentrate for acute attacks. She presented with mid to upper abdominal cramping and nausea. She had no resolution of symptoms with treatment. Her abdominal attack of 10/10 pain increased with nausea. She subsequent developed erythema marginatum.. The study was stopped 4 hours post dose. She was admitted for narcotic pain medication for symptomatic relief. The father, on Oxandrin prophylaxis, presented with abdominal attack, left hand and scrotal edema, and extensive erythema marginatum; reticular rash over the neck, back, arms, and shoulder. The attacks improved within 1 hour of treatment with significant resolution within 2 hours. The rash and abdominal symptoms resolved completely. The left hand and scrotal edema had partial resolution typical of his disease course, with continuing response up to 8 hours. HAE families have debilitating acute attacks despite prophylaxis. Replacement therapy with C1-INH concentrate is not commercially available in the United States. We treated an HAE family with DX-88 for acute attacks. Two had responses and the non responder was a potential placebo. The treatment was well tolerated. Longer follow up for safety and efficacy with ideal drug dosing are needed. Trial results are currently being analyzed. DX-88 is a promising, non plasma based, treatment for acute attacks of patients with HAE.[1][2]

Recommendation drugs for emergency treatment

All patients should have sufficient drugs for at least two attacks available at home and when traveling.

In the case of schoolchildren, teachers should be informed about the fact that attacks may occur, how these manifest, and what action needs to be taken. This information should be provided in written form.

Conclusion

The treatment of HAE, after remaining static for nearly 40 years, has undergone rapid change during the past several years; and additional drugs are likely to be approved within the next several years .

Since the time to complete resolution of an acute attack is strongly influenced by the interval between symptom onset and institution of effective therapy, early self-treatment of acute attacks may provide the best way to minimize morbidity from

breakthrough HAE attacks. The ease of use, stability and safety of icatibant are positive attributes that enhance the likelihood that it could be self-administered. While ecallantide is also administered by the subcutaneous route, the restrictions requiring administration by a health care professional would preclude self administration at this time.

Variability in attack frequency and severity, response to individual therapeutic agents, and the factors of gender, age, pregnancy, co-existing medical conditions, or access to medical care highlight the need for individualization in the approach to treatment of HAE. Ultimately, the introduction of these drugs coupled with the availability of C1 inhibitor will allow for a menu of options to incorporate into patient-centric treatment plans for HAE.

Future Developments

Work is underway to develop new treatment options in order to achieve the goal whereby HAE-C1-INH patients can lead as normal a life as possible. These potential new developments primarily relate to drugs intended for long-term prophylaxis. Developments are at various stages. Two developments are already well advanced:

The subcutaneous administration of C1-INH concentrate. Subcutaneous treatment with the Berinert derivative Haegarda for long-term prophylaxis, which has been approved in the US since 2017, has proven to be highly effective. Berinert will be available in Europe for subcutaneous use. Subcutaneous or oral treatment with novel kallikrein inhibitors Particularly in the case of long-term prophylaxis in hereditary angioedema, regular exposure of the patient to the drug over years or decades, long-term safety is especially important alongside efficacy[1]

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