

CONESTAT ALFA – A RAY OF HOPE

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INTRODUCTION

Hereditary angio-edema (HAE) is a genetic disorder that is said to occur due to the deficiency of C₁ inhibitor (a part of the classical complement activation pathway). Conestat alfa, a recombinant human C₁ inhibitor derived from the milk of transgenic rabbits, is the first non-human-serum-based treatment option available for HAE, thus making it a very radical approach to the condition.

HEREDITARY ANGIO-EDEMA (HAE)

HAE is a rare genetic disorder that was first reported in the year 1888. In the United States, the prevalence is estimated to be in the range of 1 in 10,000 to 1 in 50,000 individuals. 50% of HAE patients are

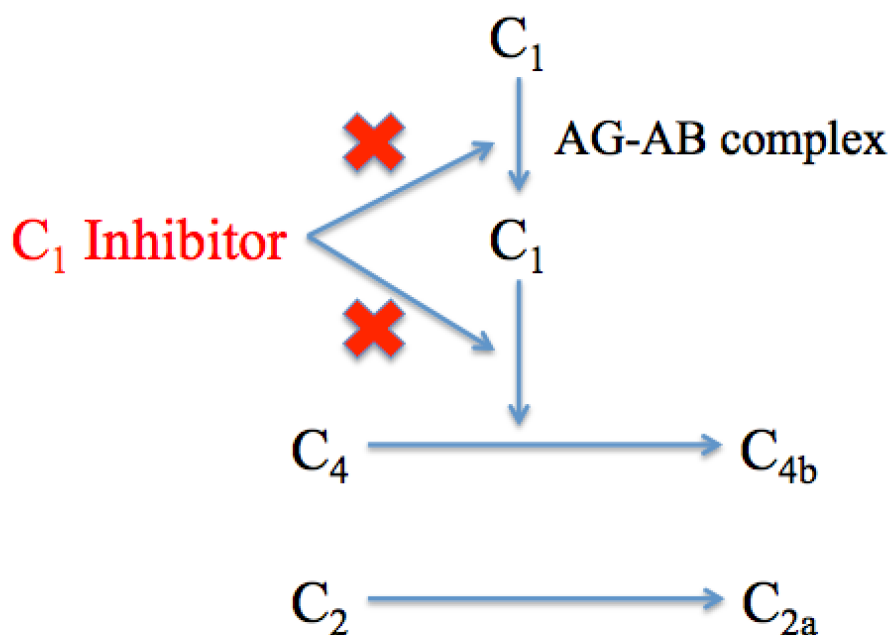
diagnosed in their first decade of life, while 30% are diagnosed in their second decade. Mortality rate in an undiagnosed HAE patient is likely to be as high as 30 to 50%.^[1]

The clinical presentation of HAE varies from mild symptoms to severe symptoms, sometimes death. The most common presentation is swelling of extremities, trunk, genitalia, face, upper respiratory tract, etc. However, the patient does not exhibit urticaria, pruritis or erythema, which could help in eliminating differential diagnoses. Abdominal manifestations, including

acute intestinal obstruction, are the second common type of presentation. Other rare forms are cerebral edema and pulmonary edema that prove fatal in most cases.^[1,2]

The leading cause of death in HAE is asphyxiation, owing to the excessive swelling of the upper respiratory tract. The frequency of attacks varies from patient to patient. Triggers like minor trauma, stress, infections and menstruation may precipitate acute attacks of HAE.^[2]

The cause for HAE is deficiency of C₁ inhibitor (C₁INH). C₁INH inhibits C₁ that plays a key role in the classical pathway of complement activation. C₁ inhibitor is physiologically synthesized in the liver, monocytes, platelets, placenta and fibroblasts. The role of C₁INH in the classical complement activation pathway is depicted below.^[2]



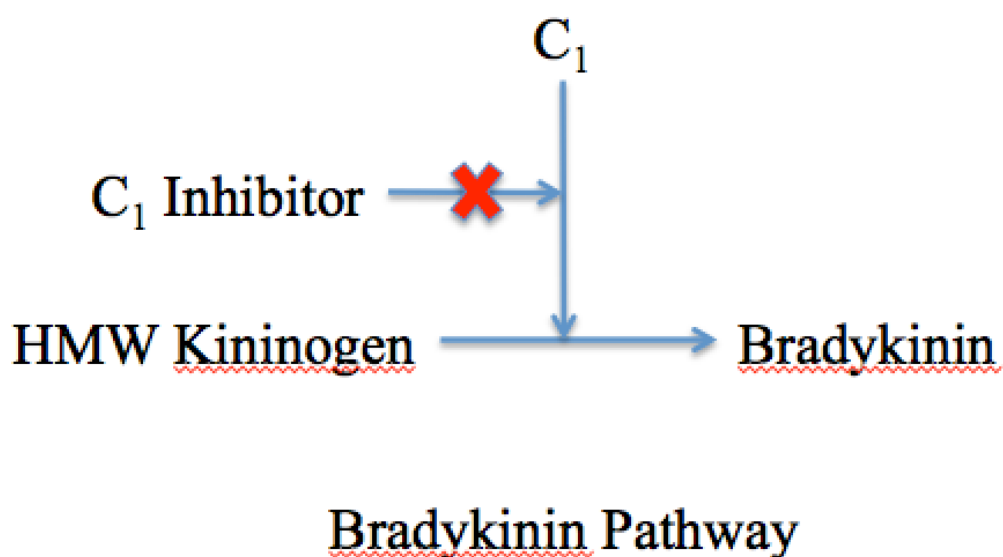
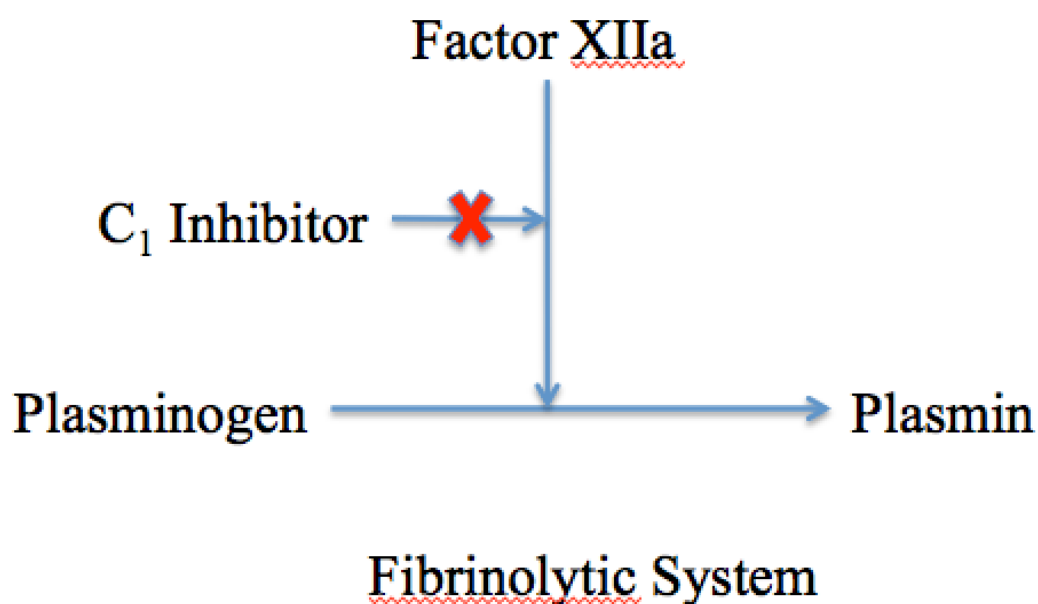
Classical Pathway of Complement Activation

There are 3 reported forms of HAE, as mentioned below.^[1,2]

- Type 1 – Quantitative deficiency of C₁INH is observed. (Around 85% of cases belong to this type)
- Type 2 – Functional deficiency/insufficiency of C₁INH is seen though the quantity synthesized is normal. (Around 15% of cases belong to this type)

- c. Type 3 – Oestrogen-dependent type that is commonly seen during pubertal spurts and pregnancy. It is also common with patients on oral contraceptives and those on hormonal replacement therapy. (Less than 1% of cases belong to this type)

In addition to inhibition of the classical complement, C₁INH also plays a role in the fibrinolytic and bradykinin pathways.



Diagnosis of HAE involves proper history taking (of patient, patient's family members, triggers), clinical examination, plasma C₄ levels, plasma C₁INH levels and genetic mapping.

EXISTING MANAGEMENT OPTIONS^[2]

1. Avoidance of triggers
2. Attenuated androgens – Stanazol, Danazol
3. Antifibrinolytics – Epsilon aminocaproic acid (EACA), Tranexamic acid
4. Fresh frozen plasma (FFP)
5. Human C₁INH replacement (approved by US FDA in 2008)
6. Plasma kallikrein inhibitor – Ecallantide, Icatibant (approved by US FDA in 2009)

CONESTAT ALFA^[1,2,3]

a. Description

Ever since the 1970s, there has been a growing need for a plasma-free source of C₁INH. Conestat alfa has satisfied this need by being the first plasma-free recombinant human C₁INH that is derived from the milk of transgenic rabbits. It functions the same way as the physiological C₁INH does, making it an ideal replacement agent in cases of deficiency of C₁INH.

b. Dosing

1 Unit of Conestat Alfa equals the amount of C₁INH present in 1 ml of fresh human plasma. It is given via intravenous route. Normal adult dosage is 50U/kg body weight, administered as slow IV dose, for every acute attack of HAE. Not more than two doses are advised in a 24-hour period.

c. Kinetics

The drug has an elimination $t_{1/2}$ of around 2 hours. It is endocytosed in the liver and then hydrolyzed or degraded. There is no renal elimination, making it safe in patients with renal impairment. However, there are no sufficient data on hepatic safety.

d. Adverse effects

- Headache
- Nausea
- Vomiting
- Vertigo

- Paraesthesia
- Swelling & urticaria at the site of injection

e. Contraindications

- Known or suspected allergy to rabbits (Confirmed by IgE testing kits)
- Hypersensitivity to the active ingredients or excipients
- Allergy to cow's milk (Cross-sensitivity may be seen)
- Pregnancy & Lactation (Not enough studies to support safety in special population)

f. Future prospects

Conestat Alfa may find itself to be useful in several other conditions in the near future. Sepsis, acute pancreatitis, acute myocardial infarction and ACE-inhibitor – induced angioedema are a few of the conditions for which the drug is being tested.

CONCLUSION

Hereditary angio-edema has been treated with human plasma-derived factors till the advent of Conestat Alfa. This novel drug offers the advantage of being free of human plasma, hence being safe from hypersensitivity reactions, blood product mismatch reactions and also lesser risk of transmission of blood-borne infections. Conestat Alfa is a radical drug in the field of immunomedicine.

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