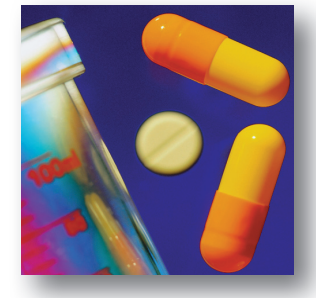

Conestat Alfa (Ruconest)

First Recombinant C1 Esterase Inhibitor for the Treatment Of Acute Attacks in Patients With Hereditary Angioedema

Martin Paspe Cruz, PharmD, CGP, BCPP, FASCP

INTRODUCTION

Hereditary angioedema (HAE) affects one in 10,000 to one in 50,000 people in the United States and Canada and contributes to 15,000 to 30,000 emergency room visits per year. HAE is a rare autosomal, dominantly inherited blood disorder caused by having insufficient amounts of a plasma protein called C1 esterase inhibitor.[1] HAE produces acute symptoms such as swelling of the face, extremities, genitals, gastrointestinal tract, and upper airways. Factors such as stress, trauma, surgery, menstruation, viral illness or infection, and some medications may trigger these acute attacks of swelling. Without immediate recognition and treatment, the swelling of the airway is life-threatening. There are three different types of the disorder: HAE type I, type II, and type III. HAE type I is the most common form, accounting for approximately 80% to 85% of the disorder. Type I results from low levels of C1 esterase inhibitors known as complements that help to control various bodily functions, such as the flow of fluids into and out of cells. Low C1 esterase inhibitor in the plasma leads to increased activation of pathways that release bradykinin, the chemical responsible for the angioedema due to increased vascular permeability, and the pain seen in people with HAE. Potential mortality rates are estimated at 15% to 33% as a result of laryngeal edema and asphyxiation.[2–4]

Drug therapy for angioedema includes histamine blockers (H_1 and H_2), steroids, and injectable epinephrine for severe and emergent conditions. However, hereditary angioedema is generally refractory to treatment with these drugs.[5,6]

Conestat alfa (Ruconest, Pharming Group/Salix Pharmaceuticals) is a human recombinant C1 esterase inhibitor purified from the milk of transgenic (genetically modified) rabbits. The drug is intended to restore the level of functional C1 esterase inhibitor in the plasma, thereby treating an acute attack of swelling.[7]

Other C1 esterase inhibitors approved for the treatment of hereditary angioedema that are plasma-derived include Cinryze (Shire) and Berinert (CSL Behring); recombinant drugs include ecallantide (Kalbitor, Dyax) and icatibant (Firazyr, Shire).[8–14]

Dr. Cruz is a Clinical Assistant Professor at the Virginia Commonwealth University/Medical College of Virginia School of Pharmacy in Richmond, Virginia, and at the Hampton University School of Pharmacy in Hampton, Virginia; an Assistant Professor of Clinical Psychiatry at the Eastern Virginia School of Medicine in Norfolk, Virginia; and a Clinical Pharmacy Specialist at the U.S. Department of Veterans Affairs Medical Center in Hampton.

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CHEMISTRY AND PHARMACOLOGY

Conestat alfa is a recombinant analogue of human complement component 1 esterase inhibitor purified from the skim milk of transgenic rabbits. It is a sterile, preservative-free, white/off-white lyophilized powder for reconstitution for intravenous injection. Conestat alfa is a soluble, single-chain glycoprotein containing 478 amino acids with a molecular mass of 68 (kDa), of which approximately 22% comprises oligosaccharide structures. One IU of recombinant human C1 esterase inhibitor (rhC1INH) activity is defined as the equivalent of C1 esterase inhibiting activity present in 1 mL of pooled normal plasma. The primary and secondary structures of the molecule and target protease selectivity are consistent with those of plasma-derived C1 esterase inhibitor (C1INH).[7]

C1INH is a serine protease inhibitor that is a normal constituent of human blood. Regulating the activation of the complement and contact system pathways is the primary function of C1INH through the formation of complexes between the protease and the inhibitor, resulting in inactivation of both and consumption of the C1INH. C1INH exerts its inhibitory effect by irreversibly binding several target proteases of the contact and complement systems. C1 inhibitor also inhibits proteases of the fibrinolytic, clotting, and kinin pathways. *In vitro* studies demonstrated the effect of conestat alfa on the target proteases, such as activated C1s, kallikrein, factor XIIa, and factor XIa. Patients with HAE typically have low levels of endogenous or functional C1INH. Attacks of angioedema in this patient population, although not clearly understood, are believed to involve contact system activation, resulting in increased vascular permeability that then leads to the clinical manifestation of HAE attacks. Contact system activation by C1INH is suppressed through the inactivation of plasma kallikrein and factor XIIa, which is thought to modulate vascular permeability by preventing the generation of bradykinin. Administration of conestat alfa increases plasma levels of functional C1INH activity.[15]

PHARMACOKINETICS AND PHARMACODYNAMICS

Pharmacokinetic evaluation of conestat alfa was performed by noncompartmental analysis, using functional C1INH levels on 12 asymptomatic HAE patients with doses ranging from 6.25 IU/kg to 100 IU/kg. Conestat alfa dose-dependently increased the plasma concentration of functional C1INH. Following administration of a 50 IU/kg dose of conestat alfa, functional C1INH was restored to levels above the lower limit of normal (0.7 IU/mL).[16] The

mean C_{max} of the drug during the study was 1.2 IU/mL with an elimination half-life of approximately 2.5 hours. The clearance of the drug was nonlinear over the dose range of 25 to 100 IU/kg.

The functional C1INH pharmacokinetics can be described by a one-compartment model with nonlinear elimination over the dose range of 25 to 100 IU/kg. Simulations predict that the recommended regimen of 50 IU/kg up to 4,200 IU will restore functional C1INH.[17]

No pharmacokinetic studies have been conducted to evaluate conestat alfa in pediatric, geriatric, renally impaired, or hepatically impaired patient populations.[15]

Conestat alfa demonstrates a dose-dependent restoration of complement homeostasis of C4 in patients with HAE. A substrate for activated C1, the complement component protein C4 is present at low levels in HAE patients. Plasma C1INH activity levels increase above the lower limit of normal, 0.7 IU/mL, following administration of a 50 IU/kg dose of conestat alfa in HAE patients.[16]

PIVOTAL CLINICAL TRIALS[7]

A randomized, double-blind, placebo-controlled trial that included an open-label extension (OLE) phase assessed the efficacy and safety of conestat alfa at 50 IU/kg in the treatment of acute angioedema attacks in HAE patients (Study 1). Subjects (N = 75) ages 17 to 69 years (63% female, 37% male; 96% Caucasian) were randomized (3:2) to receive conestat alfa 50 IU/kg (n = 44) or placebo (n = 31). Positive patient-reported responses to two questions from a treatment effect questionnaire (TEQ), along with continued improvement at the next assessment, were the primary efficacy endpoints of the study. TEQ is a seven-point scale used to assess the patient's severity of attack symptoms at affected anatomical locations, as well as whether symptoms decreased after the treatment drug was administered. For patients with no relief after four hours of the study drug administration and patients who experienced life-threatening oropharyngeal-laryngeal angioedema symptoms, a rescue treatment of conestat alfa was made available during the clinical trials. Among patients who received the rescue treatment, the time to beginning of relief of symptoms was screened out at the last assessed time prior to medication use. The median time to the beginning of relief of symptoms was significantly shorter in patients treated with conestat alfa 50 IU/kg at 90 minutes (95% confidence interval [CI], 61–150, n = 44) compared with patients treated with placebo at 152 minutes (95% CI, 93–not estimable [NE], n = 31).

Among U.S. patients, the median time to the beginning of relief of symptoms with persistence at the primary attack location was 98 minutes in patients treated with conestat alfa [95% CI, 45–240, n = 22] compared with 90 minutes in patients treated with placebo [95% CI, 50–NE, n = 16]. The hazard ratio (HR) for the time to the beginning of relief of symptoms in this subgroup was 1.20 (95% CI, 0.48–3.01) for the treatment group compared with the placebo group. The median times to the beginning of symptom relief for non-U.S. patients were 90 minutes (95% CI, 63–120, n = 22) and 334 minutes (95% CI, 150–50, n = 15) in subjects receiving the treatment drug and the placebo, respectively. The HR for this subgroup was 4.82 (95% CI, 1.58–14.72) for patients receiving the treatment drug compared with placebo.

The median time to the beginning of relief in women was 113 minutes (95% CI, 63–151, n = 28) in the treatment group and 105 minutes (95% CI, 60–334, n = 19) in the placebo group, with a HR of 1.22 (95% CI, 0.60–2.48) for treatment versus placebo. The median time to the beginning of relief was 75 minutes (95% CI, 45–210, n = 16) and 480 minutes (95% CI, 150–50 , n = 12) for men in the treatment and placebo groups, respectively. The HR for men in the treatment group versus placebo was 3.94 (95% CI, 1.23–12.68).

The efficacy of conestat alfa 50 IU/kg for different anatomical locations of HAE attacks is shown in Table 1.

A total of 44 patients from Study 1 were enrolled into the OLE phase and treated with conestat alfa 50 IU/kg for a total of 170 HAE attacks. The study demonstrated that the efficacy of conestat alfa 50 IU/kg was maintained over repeated attacks of HAE. The median time to the beginning of relief of symptoms in this phase was 75 minutes (95% CI, 64–90). A second dose of conestat alfa 50 IU/kg was administered to five subjects (3%) during the OLE phase of Study 1.

Two additional randomized controlled trials, Study 2 (North American) and Study 3 (European), were conducted to establish the safety and efficacy of conestat alfa. Subjects in Study 2 (17–66 years of age; 74% female, 26% male; 92% Caucasian) were randomized to receive a single administration of either conestat alfa 50 IU/kg (n = 12), conestat alfa 100 IU/kg (n = 13), or placebo (n = 13). Patients in Study 3 (17–71 years of age; 53% female, 47% male; 100% Caucasian) were randomized to receive a single administration of either conestat alfa 100 IU/kg (n = 16) or placebo (n = 16). A visual analog scale (VAS) was used in assessing patients' symptoms; a VAS decrease of more than 20 mm compared with baseline, with persistence of the improvement at two consecutive time points, was considered the onset of relief in both studies. The efficacy of the treatment drug in the treatment of acute angioedema attacks for both studies was demonstrated by significantly shorter times to the beginning of symptom relief based on the VAS. OLE studies of 119 subjects treated with conestat alfa in a total of 362 acute angioedema attacks also demonstrated continued efficacy during repeat attacks.

SAFETY PROFILE

Contraindications

Conestat alfa is contraindicated in patients with a history of allergy to rabbits or rabbit-derived products and in patients with a history of life-threatening immediate hypersensitivity reactions, including anaphylaxis, to C1 esterase inhibitor preparations.[15]

Table 1 Proportion of Patients Who Achieved Relief Within Four Hours, By Attack Type[15]

Attack Type	Ruconest 50 IU/kg n/N (%)	Placebo n/N (%)
Abdominal	14/16 (88%)	7/12 (58%)
Facial	3/6 (50%)	0/2 (0%)
Peripheral (extremities)	17/20 (85%)	7/14 (50%)

Warnings and Precautions

Severe hypersensitivity reactions, including anaphylaxis, may occur when conestat alfa is administered. Symptoms may include hives, generalized urticaria, chest tightness, wheezing, hypotension, and/or anaphylaxis during or after injection of the drug. Discontinue the drug when these symptoms occur. Thromboembolic events have been reported in patients with risk factors, such as an in-dwelling catheter/access device, history of thrombosis, atherosclerosis, use of contraceptives or certain androgens, obesity, and immobility, at recommended doses of plasma-derived C1 esterase inhibitor. Patients with known risk factors for thromboembolic events should be monitored while and after receiving the drug.[15]

Adverse Reactions

Anaphylaxis was the most serious adverse reaction during the clinical studies of conestat alfa. Headache, nausea, and diarrhea were the most common adverse reactions (2% or more) reported in the studies. Other adverse reactions reported were angioedema, sneezing, erythema marginatum, back pain, a sensation of burning skin, vertigo, lipoma, abdominal pain, and rash. Abnormal laboratory values have been reported, such as increased C-reactive protein and increased fibrin D-dimer.[15]

Immunogenicity

Immunogenicity is a potential adverse effect of conestat alfa administration based on pre-exposure and post-exposure samples from 205 HAE patients who were given the drug for 650 acute attacks. Patients were tested for antibodies against plasma-derived C1INH or rhC1INH and for antibodies against host-related impurities (HRIs). Testing was performed prior to and after treatment of a first attack and subsequent attacks at seven, 22 or 28, and 90 days after drug treatment. The frequency of anti-C1INH antibodies varied from 1.2% to 1.6% and 0.6% to 1.0% of tested samples that were taken prior to the first exposure and after the first exposure to conestat alfa, respectively. The frequency of anti-C1INH antibodies varied from 0.5 to 2.2% in samples tested after repeated exposures. In pre-exposure samples, the frequency of anti-HRI antibodies was 1.0%, while the frequency varied from 3.5% to 4.6% after the first exposure. The frequency of anti-HRI antibodies varied from 5.7% to 17% in samples after repeated exposure. After treatment for five HAE attacks, at least 10% of patients developed specific antibodies to conestat alfa. Anti-C1INH neutralizing antibodies were not detected during the studies and no adverse clinical findings were linked to the observed anti-C1INH and anti-HRI antibodies during the studies. Comparison of the incidence of antibodies to conestat alfa with other, similar products may be misleading because of several factors involved in the process, such as the assay methodology, sample handling and collection, drug interactions, and comorbid disease states.[15]

Drug Interactions

No drug interactions were studied during the clinical trials. Per the manufacturer, do not administer the drug with other intravenous drugs.

Pregnancy and Nursing

Conestat alfa is a pregnancy Category B drug and should only be used during pregnancy if indicated. Animal studies conducted at doses up to 12.5 times the human dose of 50 IU/kg could not exclude an effect on embryofetal development. More adequate and well-controlled studies are needed to determine the product's safety in pregnant women during acute HAE attacks. Administration of conestat alfa during labor and delivery has not been studied; therefore, use only if indicated. It is unknown if the drug is excreted in human milk, so caution should be exercised when the drug is administered to a nursing mother.

DOSAGE AND ADMINISTRATION

The recommended dose of conestat alfa for an acute HAE attack is 50 IU/kg for patients weighing less than 84 kg up to 4,200 IU for patients weighing 84 kg or more, to be administered as a slow intravenous injection over five minutes. An additional dose of the same recommended amount can be administered if symptoms persist, but do not exceed two doses in 24 hours.

Conestat alfa is available as a lyophilized powder for reconstitution for injection in a single-use 25-mL glass vial containing 2,100 IU of rhC1INH per vial. Reconstitute the conestat alfa with 14 mL of sterile water for injection. Slowly swirl the vial to mix; avoid foaming. The solution should be colorless, clear, and free from visible particles after reconstitution and prior to administration. The reconstituted product should be used immediately but can be stored within eight hours at 2° C to 8° C (36° F to 46° F). The solution cannot be mixed with other intravenous products and should be administered by a separate infusion line.

Pediatric Use

The safety and efficacy of conestat alfa were studied in 17 subjects from 13 to 17 years of age treated for 52 HAE attacks. About 47% (seven) adolescent patients experienced adverse reactions such as abdominal pain, headache, and oropharyngeal pain. No serious adverse effects were noted.

Geriatric Use

A total of seven geriatric patients were included in the studies, an insufficient number to determine if this age group will respond differently than younger subjects.

P&T COMMITTEE CONSIDERATIONS

Administration of human C1 esterase inhibitor is the most widespread treatment strategy for patients with hereditary angioedema. The addition of conestat alfa to the hospital formulary may be a viable option considering its unique mechanism of action and may decrease the length of stay during hospitalization. One cost-utility analysis was conducted comparing conestat alfa and Berinert P in acute, life-threatening angioedema attacks. It found that administration of conestat alfa was economically justified from the Polish health care payer's perspective, resulting in lower costs and higher cost-utility probability compared with Berinert P.[18]

COST

The average wholesale price of a vial containing 2,100 IU of Ruconest, supplied as a powder for solution, is $5,700.[19]

CONCLUSION

Conestat alfa is the first recombinant C1 esterase inhibitor approved in the United States for the treatment of acute

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attacks in patients with hereditary angioedema, which affects thousands of people annually. Further studies are needed in special populations (i.e., geriatric and pediatric), as well as in patients with comorbid states such as end-stage renal disease and hepatic impairment.

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