Immuno-Safety of Recombinant Human C1 Inhibitor in Patients With Hereditary Angioedema: An Integrated Analysis

Erik Hack, MD, PhD,1 Anurag Relan, MD,2 Leonard Kaufman, PhD,3 and Rienk Pijpstra, MD4
1Department of Immunology, Dermatology/Allergology & Rheumatology, University Medical Center, Utrecht, Utrecht, Netherlands; 2Pharming Technologies BV, Leiden, Netherlands; 3Yeeda Clinical Research, Brussels, Belgium.

Background: Recombinant C1 inhibitor (rhC1INH) is a novel therapeutic option for the treatment of acute angioedema attacks in patients with hereditary angioedema (HAE). The amino acid sequence of rhC1INH is identical to that of endogenous C1INH. However, any recombinant protein may elicit antibodies against the protein and/or host related impurities (HRI). Clinical consequences of these antibodies can theoretically range from no clinical symptoms to allergic reactions and reduced C1INH activity due to neutralizing antibodies.

Objective: To analyze the immuno-safety of rhC1INH in symptomatic patients with HAE.

Methods: Plasma samples were collected pre-treatment and 22 and 90 days post-treatment of an acute angioedema attack. Plasma samples were tested for the presence of antibodies against plasma-derived C1INH and rhC1INH using 6 different, validated enzyme-linked immunosorbent assays (ELISAs), to detect IgM, IgG, and IgA antibodies against plasma-derived C1INH or rhC1INH. Antibodies against HRI in plasma samples were measured in an ELISA testing for all antibody classes. Plasma samples from normal healthy controls and HAE patients, never exposed to rhC1INH, were used to estimate cut-off levels of the assays. Plasma samples with antibody levels above the cut-off level in the screening assays were tested in confirmatory displacement assay in case of anti-HRI antibodies and in an assay for neutralizing antibodies in case of antibodies against C1INH.

Results: Data from 155 symptomatic HAE patients having received a total of 424 administrations of rhC1INH were analyzed. The frequency of anti-C1INH antibody levels above the assay cut-off was low and similar in pre- and post-exposure samples (1.7 and 1.8%, respectively). Results above the assay cut-off were sporadic and transient. Occurrence of anti-C1INH antibodies did not correlate with repeated treatment or time since last treatment. No neutralizing antibodies were detected. A total of 5/155 (3%) rhC1INH-treated patients had confirmed anti-HRI antibodies; these included 1 patient with presence of anti-HRI antibodies prior to exposure to rhC1INH. The presence of anti-C1INH and anti-HRI antibodies was not associated with clinical symptoms. The presence of anti-C1INH antibodies did not affect clinical efficacy.

Conclusions: rhC1INH used for the treatment of acute HAE attacks has a low potential to induce antibodies and has a reassuring immuno-safety profile.

The Efficacy and Safety of Human Plasma-derived C1-Inhibitor Concentrate Administered for the Treatment of Attacks in Pediatric Patients with Hereditary Angioedema Due to C1-Inhibitor Deficiency

Henriette Farkas, MD, PhD, DSc,1 Dorottya Csuka, PhD,1 Zsuzsanna Zotter,1 Érika Szabó, MD,1 Zsuzsanna Kelemen, MD,1 Lilian Varga, PhD,1 János Fejes, MD,2 and George Harmat, MD2
13rd Department of Internal Medicine, Semmelweis University, Budapest, Hungary; 2Pediatric Department, Budapest, Hungary.

Background: Hereditary angioedema due to C1-inhibitor deficiency (HAE-C1-INH) is a life-threatening, rare disease characterized by recurrent edematous attacks. In 50% of cases, the initial onset of symptoms occurs between 5 and 11 years of age. There are limited data on the emergency treatment of acute episodes in pediatric patients. Our aim was to analyze the efficacy and safety of human plasma-derived C1-INH concentrate in our pediatric patient population with HAE-C1-INH.

Methods: 50 pediatric patients (23 boys, 27 girls; 45 HAE type I, 5 HAE type II patients) were enrolled. The follow-up period began at the time of diagnosis and ended when the patient turned 18 years old. The indications for the use of
C1-INH concentrate were upper airway oedema of any severity; moderate-to-severe abdominal edema; edema of face, neck, or lips and severe edema of the extremities and trunk. Clinical and laboratory data were entered into the Hungarian HAE Registry.

**Results:** 152 attacks out of 1392 experienced by 42 patients were treated with C1-INH concentrate (28% of attacks at home and 72% at the clinic). The distribution of C1-INH-treated attacks by location was as follows: 38% subcutaneous, 32% abdominal, 30% upper airway. In all locations, the clinical symptoms were consistently relieved by 300 IU C1-INH concentrate. An additional 500 IU dose of C1-INH concentrate was required in 4 cases only. The symptoms improved within 15 to 60 minutes of drug administration. Time to complete resolution was 24 to 48 hours in subcutaneous edema, 12 to 24 hours in abdominal attacks, and less than 12 hours when the edema involved the upper airways. No progression or recurrence of the attack was observed. Repeated administration did not reduce therapeutic efficacy of the drug. Adverse events did not occur. Transmission of viral infections (HIV, HBV, HBC, Parvo virus B19) was not detected. Comparing the first and last year of follow-up, anti-C1-INH antibodies (IgA, IgG, IgM types) did not show any relationship with the administration of C1-INH concentrate.

**Conclusions:** Our prospective study demonstrated that the administration of C1-INH concentrate is highly effective and safe for the treatment of edematous attacks – regardless their location – in pediatric patients with HAE-C1-INH.

---

### 87 Treatment of Idiopathic Nonhistaminergic Angioedema with Icatibant

Ramon Lleonart, MD,1 Blanca Andres, MD,1 Javier Jacob, MD,2 Lourdes Pasto, MD,3 and Mercé Corominas, MD,1 1Allergy Unit; 2Emergency Department, and; 3Pharmacy Service, Hospital Universitari de Bellvitge, L’Hospitalet de Llobregat, Spain.

**Background:** Patients with Idiopathic nonhistaminergic angioedema appear to have similar clinical features and pathogenesis as those with hereditary angioedema. Icatibant, a selective bradykinin B2 receptor antagonist, licensed for use in acute attacks of hereditary angioedema could be also effective in treating other forms of angioedema. We report a patient with idiopathic angioedema who was successfully treated with icatibant.

**Methods:** A 77-year-old man with a history of arterial hypertension currently treated with hydrochlorothiazide and type II diabetes under insulin treatment. He had suffered from recurrent angioedema attacks located on his tongue without urticaria during the last 7 years. Serum levels of C1-INH, C4 and C1q activity were normal. In spite of cessation of treatment with ACE inhibitors and RAAS-blockers (he had been treated with enalapril and losartan previously) he continued with the angioedema attacks. As no cause of angioedema could be identified and the angioedema did not respond to antihistamines, the patient was diagnosed of idiopathic nonhistaminergic angioedema. In one of the episodes he was admitted at the emergency room with a swollen tongue. The edema gradually progressed in spite of the treatment with antihistamines, corticosteroids and epinephrine. Tracheotomy was considered due to the severity of the angioedema that began to cause airway compromise. After consulting the Allergy Unit, treatment with icatibant was administered.

**Results:** Approximately 30 minutes after the subcutaneous administration of icatibant 30 mg the symptoms improved and the angioedema resolved completely within 6 hours. The only adverse effect following the icatibant administration was pain localized in the injection site. After 5 months the patient suffered a similar attack that was also successfully treated with icatibant sc.

**Conclusions:** Icatibant administered subcutaneously provided an effective and well-tolerated treatment option for acute angioedema attacks in a patient with idiopathic nonhistaminergic angioedema. This form of angioedema could have a pathogenic mechanism similar to the bradikinin mediated angioedema. We suggest the use of icatibant in the treatment of severe attacks of angioedema in patients that do not respond to antihistamines, corticosteroids and epinephrine.

---

### 88 Clinical Features and Diagnostic Value of Specific IGE to Component Allergen in Bee Venom Allergy in Korea

You Seob Shin, MD, PhD,1 Jing Nan Liu,1 Young-Hee Nam, MD,1 Hyun-Jung Jin, MD,1 Young-Min Ye,1 Dong-Ho Nahm,1 and Hae-Sim Park, MD, PhD,1 1Department of Allergy and Clinical Immunology, Ajou University School of Medicine, Suwon-si, South Korea; 2Internal Medicine, Korea University College of Medicine, Seoul, South Korea.

**Background:** Although history taking is primary method in the diagnosis of bee venom allergy, serum specific IgE detection is critical to identify causative bee and assess the effect of immunotherapy. Component-resolved diagnosis (CRD) in allergy has been used for its high sensitivity and specificity in many allergy diseases caused by food, cat, birch, and grass pollens. The purposes of this study are to evaluate diagnostic value of serum specific IgE to 3 bee venom component allergens and observe the changes of allergen specific IgE during bee venom immunotherapy.

**Methods:** Fifty-six bee venom anaphylaxis patients receiving bee venom immunotherapy were recruited from Ajou University Hospital. Clinical manifestations and serum specific IgE levels to bee venoms and component allergens (rApi m1 of Apidae, rVes v5 and rPol d5 of Vespidae) measured by using ImmunoCAP (Phadia, Sweden) were analyzed retrospectively.

**Results:** Thirty-five (62.5%) patients were male and 33 (73.3%) were atopic. Their mean age was 44.9 ± 13.8 years ranged from 11 to 73 years. Local reactions were found in 13 (23.2%) patients, while systemic reactions, in 43 (76.8%) patients. The most frequent manifestation was anaphylaxis which were severe (37.5%) and moderate (39.3%) manifestations followed by urticaria and angioedema. Yellow Jacket (80.8%) was the most prevalent bee followed by yellow hornet, white faced hornet, honey bee and paper wasp at the time of diagnosis with concurrent sensitization in both Apidae and Vespidae at 70.9% patients. The positive predictive value (PPV) of serum specific IgE levels to rVes v5 and rPol d5 were 85.7 and 87.5%, and they significantly correlated with conventional serum specific IgE level (r = 0.762 and r = 0.757, respectively), however, PPV of rApi m1 was only 34.8% at the time of initial diagnosis. After 3 years of bee venom immunotherapy, all kinds of bee venom specific IgE levels tended to decline compared to those collected before allergen immunotherapy, especially in component specific IgE to Vespidae.

**Conclusions:** Yellow jacket sting and male gender may be risk factors for bee venom allergy in Korea. Component allergen specific IgE to Vespidae, not Apidae had a diagnostic and monitoring value comparable to conventional specific IgE in bee venom allergy.

---

### 89 Is Basophil Specific Response to Hymenoptera Venom Related to T Regulatory Cells?

Petr Kucera, MD,1 Katarina Hulikova,2 Milada Cvakova, MD,1 Daniela Pianska,1 and Kamila Riegerova,1 1Department of Allergy Immunology, 3rd Medical Faculty Charles University, University Hospital KV, Prague, Czech Republic; 2Department of Allergy Immunology, 3rd Medical Faculty, CHU, Prague, Czech Republic; 3Department of Allergy Immunology, 3rd Medical Faculty, Charles University, Prague, Czech Republic.

**Background:** The exact mechanism of systemic hypersensitivity to venom is not exactly understood. It is suggested T cells with regulatory potential can downregulate other T cell subsets and effector cells, ex. mast cell or