

**Successful Use of Recombinant Human C1-INH in a Patient with Acquired Angioedema due to C1 Inhibitor Deficiency and an Unusually High Titer of Anti-C1-Inhibitor Autoantibodies**

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**Key words:** Acquired angioedema. Anti-C1-INH autoantibodies. Recombinant human C1-inhibitor.

**Palabras clave:** Angioedema adquirido. Autoanticuerpos anti-C1-INH. C1 inhibidor recombinante humano.

Recurrent angioedema (AE), in particular bradykinin mediated forms, represent a genuine diagnostic and therapeutic challenge. Two forms can be distinguished: hereditary (HAE) and acquired (AAE). In the most common case, AAE is associated with the use of angiotensin-converting enzyme inhibitors (ACEi). Acquired deficiency of C1-INH (C1-INH-AAE) may be another, but rarer cause of AAE. Various mechanisms in acquired C1-INH deficiency have been described and are predominantly linked to underlying diseases, such as lymphoproliferative disorder or autoimmune disease [1]. In certain patients, both mechanisms (e.g. increased consumption of C1-INH in the background of lymphoproliferative disease and the presence of anti-C1-INH autoantibodies) could simultaneously participate on the pathophysiology of C1-INH-AAE and the development of clinical symptoms [2].

We present the case of a 67-year-old man with an acquired form of angioedema due to C1-INH deficiency, with an unusually high titer of specific autoantibodies against C1-INH. The patient was referred to our Center with recurrent non-pruritic angioedema of the face, lips, tongue and submucosal edema in the larynx associated with dyspnea, which required intubation. No family history for recurrent angioedema or allergies was evident. The patient had been treated in the past for arterial hypertension with ACEi (5 mg of ramipril per day). Discrete symptoms of angioedema were present before the treatment with ACEi, which increased the frequency and partially also the severity of AE. Due to a recurrent angioedema and cough, the ACEi was switched to amlodipine. However, the angioedema persisted, and its intensity and frequency gradually increased even after the cessation of ACEi treatment. The

angioedema was treated with antihistamines (single and fourfold increase in dose) and systemic corticosteroids, however, without any clinical impact. Due to second-degree atrioventricular blockage and paroxysmal supraventricular tachycardia, the patient underwent cardiac pacemaker implantation. After this intervention, the patient experienced his first attack of laryngeal angioedema with intubation and was referred to our Center. The initial laboratory examination revealed a significantly decreased concentration and function of C1-INH and decreased concentration of C4 and C1q complement components. The diagnosis of acquired angioedema with C1-INH deficiency was established through two separate measurements in three months (**Table 1**). Hematological examination excluded any hematological diseases. Indirect fluorescence showed a strong presence of antinuclear antibodies (coarse speckled pattern) and anti-dsDNA (62 U/mL, normal range < 20 U/mL) using ELISA. The patient did not show any signs of clinical rheumatic diseases. An examination for autoantibodies against C1-INH was conducted in the Complement Laboratory at Semmelweis University (Budapest). A high titer of anti-C1-INH IgG (35.00 U/mL, normal range: 0–2 U/mL) was detected, and a diagnosis of C1-INH-AAE type 2 was established (**Table 1**). Due to the patient's history of venous thrombosis (contraindication for antifibrinolytics), a successful prophylactic treatment of attenuated androgens was initiated (200 mg of danazol once daily). The breakthrough angioedema attacks were treated with recombinant human C1-INH (rhC1-INH). Up to now, six attacks of facial angioedema and four attacks of laryngeal angioedema had been treated with 2100 U (body weight 92 kg), showing significant improvement 0.5–2 hours after treatment and complete resolution of AE symptoms in 12–24 hours.

Acquired angioedema with C1-INH deficiency shares the same clinical presentation as other types of bradykinin mediated angioedemas, although its etiology is completely different. Moreover, the clinical symptoms of C1-INH-AAE could precede the diagnosis of the

underlying disease. The detection of autoantibodies against C1-INH is useful, however, only a few laboratories can provide this examination since commercial kits are not available [3]. Moreover, it appears that anti-C1-INH autoantibodies may have the capacity to predict the response to therapy with C1-INH concentrate [2].

Therapies regulating kallikrein and bradykinin activity are recommended. Treating the underlying condition is also recommended. For long-term prophylactic treatment, tranexamic acid, attenuated androgens or plasma derived C1-INH can be used. Antifibrinolytic agents seem to be more effective compared to HAE [4]. Androgens are effective only in a small proportion of C1-INH-AAE patients. For the most severe patients, regular administration of plasma derived C1-INH can be selected. The need for higher doses of pdC1-INH were reported due to the presence of anti-C1-INH autoantibodies in some patients [2]. The successful use of icatibant and ecallantide has also been published [5].

The expression of AAE could be in certain cases precipitated by the use of ACEi. In a proportion of the patients clinical symptoms of AE could persist even after the cessation of the ACEi treatment [6]. Up to now, only two case reports of AAE treated with recombinant C1-INH concentrate have been reported. In the case studies of Manson et al. (2014), one patient with AAE was treated with 4200 U of rhC1-INH for an abdominal and facial angioedema attack. Previous treatment with pdC1-INH (even at a dose of 1000–1500 U) failed and was not effective. The symptoms after treatment with rhC1-INH improved within 1 hour, although after 12 hours, new abdominal pain and facial swelling developed. No information about anti-C1-INH autoantibodies can be extracted from the publication [7]. Another case report showed excellent efficacy of rhC1-INH in treating laryngeal attacks with negative anti-C1-INH-autoantibodies in a patient with C1-INH-AAE Type 1 [8]. We initially used lower dose for the treatment of the AE attack (2100 IU). Since this was successful and fully effective, we used the same dose also for the next attacks, without the decline of clinical

efficacy. It seems that compared to pdC1-INH, rhC1-INH could carry lower risk for the formation of neutralizing antibodies. In a study of 155 HAE patients treated with repeated rhC1-INH application, the anti-rhC1-INH were detected in 6 of them (in 1 patient pre-existing before the first treatment). No neutralizing antibodies against rhC1-INH were found [9]. Moreover, rhC1-INH possesses different glycosylation profile compared to pdC1-INH and does not contain neuraminic acid [10].

We report a successful, repeated application of recombinant human C1-INH concentrate in a patient with C1-INH-AAE type 2 due to unusually high anti-C1-INH autoantibodies of IgG isotype. It can be concluded that rhC1-INH may be an effective alternative treatment for angioedema attacks in these patients, even with the presence of anti-C1-INH antibodies.

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### **Conflict of interests**

MJ – received grants from CSL Behring, Shire/Takeda and Pharming and served as an advisor for these companies and participated in clinical trials/registries for BioCryst, CSL Behring, Pharming, and Shire/Takeda.

MB – does not have any potential conflict of interests

PB – participated in clinical trials/registries for BioCryst, CSL Behring, Pharming, and Shire/Takeda.

LV – does not have any potential conflict of interests

HF – received grants from CSL Behring, Shire/Takeda and Pharming and served as a advisor for these companies and BioCryst, and participated in clinical trials/registries for BioCryst, CSL Behring, Pharming, Kalvista and Shire/Takeda.

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**Table 1:** Selected laboratory parameters of the presented patient. The interval between the two samples was three months. Treatment with androgens commenced during this period and improved the selected parameters in the second sample.

Parameter	Result		Normal Range	Dimension	Evaluation
	1	2			
<b>C3</b>	2.03	1.5	0.90–1.80	g/L	H/N
<b>C4</b>	<b>0</b>	<b>0.14</b>	0.15–0.55	g/L	L
<b>C1 inhibitor concentration</b>	<b>0.08</b>	<b>0.13</b>	0.15–0.30	g/L	L
<b>C1 inhibitor functional activity</b>	<b>0</b>	<b>89</b>	70–110	%	L/N
<b>C1q</b>	<b>3</b>	<b>115</b>	60–180	mg/L	L/N
<b>Anti-C1-INH IgG</b>	<b>35</b>	<b>39</b>	0–2	U/mL	H
<b>Anti-C1-INH IgA</b>	<b>0.07</b>	<b>0.07</b>	0–0.6	U/mL	N
<b>Anti-C1-INH IgM</b>	0	0.02	0–12	U/mL	N
<b>Anti-C1q IgG</b>	5	6	0–52	U/mL	N

H = higher than normal, L = lower than normal, N = normal