

Idiopathic Non-histaminergic Angioedema: Successful Treatment with Omalizumab in Five Patients

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Abstract Idiopathic non-histaminergic acquired angioedema (InH-AAE) is a rare disease characterized by AE resistant to antihistamines and a chronic course. We report five new cases of InH-AAE (two women and three men) with a rapid and dramatic response to the anti-immunoglobulin-E antibody omalizumab. In our literature review, we found 13 other relevant cases with a good response to this treatment. Overall, in 6 out of 18 patients, the doses of omalizumab required to prevent recurrences of attacks were higher than the licensed dose for chronic urticaria. No significant adverse effects have been reported.

Keywords Idiopathic angioedema · non-histaminergic angioedema · omalizumab

Introduction

Angioedema (AE) is a self-limiting swelling of the hypodermis or the submucosal tissue, which spontaneously regress

within a few hours or days [1]. This symptom is related to an increase in capillary permeability and primarily caused by mast cell degranulation or activation of the kinin-kallikrein system [2].

Mast cell-mediated AE is the most common form of AE, either due to allergic (IgE-mediated) or non-allergic mast cell activation [2]. In chronic spontaneous or idiopathic urticaria (CSU/CIU), a skin disease characterized by the recurrence of transient wheals, about 50 % of patients suffer from AE attacks [3, 4].

In the case of patients suffering from AE without urticaria, several diseases can be discussed [5, 6]. An international consensus was held in 2012 to refine the definitions of the disease entities, and four acquired forms of AE have been separated: idiopathic histaminergic AE (IH-AAE), idiopathic non-histaminergic AE (InH-AAE), acquired AE related to angiotensin-converting enzyme inhibitors (ACEi-AAE), and AAE with C1-inhibitor deficiency (C1-INH-AAE) [6]. By definition, IH-AAE is a type of AE without wheals whose recurrences respond to a continuous administration of antihistamines, whereas in InH-AAE, recurrences persist [6, 7].

Omalizumab is a humanized anti-IgE antibody, which inhibits its binding to the FcεR-1. Its efficacy and safety in CSU/CIU resistant to antihistamines with or without angioedema has been demonstrated in several randomized placebo-controlled studies [8–11].

Because of the resistance to antihistamines in InH-AAE, it has been suggested that bradykinin is involved, but evidence is still lacking [6, 12, 13]. Against this hypothesis, cases of successful treatment with omalizumab in patients suffering from InH-AAE have already been reported, suggesting a mast cell-mediated mechanism, as described in patients with IH-AAE and CSU/CIU [14–16].

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We report here a series of five patients suffering from idiopathic recurrent AE non-responding to antihistamines treated with omalizumab.

Case Report

Patient 1 is a 35-year-old white woman who had recurrent AE without wheals for 4 years. She experienced swellings of her lips, cheeks, and tongue, and unexplained abdominal pains at least twice weekly. She had been treated neither with angiotensin-converting enzyme inhibitors (ACEi) nor angiotensin receptor blockers (ARB) nor gliptins. She could not relate the AE attacks to any trigger. Physical examination was unremarkable. Her symptoms did not improve during administration of different H1-antihistamines with increased dosage up to fourfold of the daily dose. Laboratory tests, including complete blood count (CBC), thyroid stimulating hormone (TSH), anti-thyroperoxidase antibody (anti-TPO Ab), C4 level, and C1 inhibitor function and level, were within the normal range. Her total IgE level was 127 kU/l (0–150 kU/l). She was proposed a treatment regimen with omalizumab as add-on therapy to anti-H1 antihistamines, according to the current guidelines for patients suffering from CSU/CIU (300 mg of omalizumab repeated monthly). Because of the recurrence of symptoms a few days before the next injection, the treatment cycle was shortened by 2 weeks. With a treatment interval of 2 weeks, she remained free of AE attacks and abdominal pains for 12 months.

Patient 2 is an 88-year-old woman who had almost weekly recurrent severe angioedema attacks in her face (lips, chin, cheeks), tongue, and limbs for 33 years. Urticaria was absent. She had been prescribed neither ACEi nor ARB nor gliptins nor hormone replacement therapy. She had failed to respond to several treatments in the past including antihistamines up to the fourfold dose and to corticosteroids. Laboratory findings included normal values for CBC, antinuclear antibody, TSH, C4 level, and C1 inhibitor level and function, and total IgE level of 58 kU/l (0–150 kU/l). In 2016, a treatment with 300 mg of subcutaneously administered omalizumab every 4 weeks was begun. Because of the recurrence of attacks in the third week, the treatment interval had been shortened to one injection each other week. When using this treatment scheme, she was free of AE attacks for 3 months.

Patient 3 is a 49-year-old man presenting with a chronic recurrent AE in the lips, cheeks, tongue, and external genital organs. Initially, he had weekly attacks of AE without urticaria or pruritis. He could not relate the AE attacks to any trigger and physical examination was unremarkable. He had no history of treatment with ACEi or ARB or gliptins. No response to antihistamines was observed even at the fourfold dose.

During the management of acute attacks, he had already received corticosteroids (methylprednisolone), C1-inhibitors, and icatibant with no response. Laboratory results included normal values for complete blood count, TSH, anti-TPO Ab, and C1 inhibitor function and level, and total Ig E level of 149 kU/l (0–150 kU/l). In 2012, a treatment with 300 mg of omalizumab monthly was begun. The retreatment interval had to be shortened to 3 weeks because of several late recurrences (during the third week). In April 2016, the patient was still free of AE attacks.

Patient 4 is a 46-year-old man with a history of childhood asthma who had recurrent AE of his lips, tongue, hands, and feet since 2012. He had never exhibited wheals. Most of attacks regressed within 12 h. One attack involving the upper airway had been efficiently treated with intramuscular adrenaline. He had no history of treatment with ACEi or ARB or gliptins. Physical examination and laboratory tests, including C1 inhibitor level and function, were unremarkable. A trial of up to fourfold dose of H1-antihistamine was not successful to prevent recurrences, and he was proposed omalizumab 150 mg twice monthly. Then, a complete resolution of symptoms was observed. Omalizumab was stopped in April 2015. In August 2015, he exhibited a relapse of his AE with daily attacks in his face, feet, and hands. In September 2015, omalizumab was resumed (300 mg monthly) with a complete resolution of symptoms. Until April 2016, the patient remained free of AE attacks.

Patient 5 is a 39-year-old man with a family history of chronic urticaria. In 2013, he had recurrent AE attacks in his face, tongue, larynx, upper limbs, and external genital organs. Two attacks occurred following dental work. He never exhibited wheals. He had never been prescribed ACEi or ARB or gliptins. Laboratory findings included normal values for CBC, antinuclear antibody, C1 inhibitor level and function, and total Ig E level of 299 kU/l (0–150 kU/l). Short courses of corticosteroids were efficient to relieve symptoms. Background treatments with antihistamines at up to four times the normal dose or tranexamic acid did not have a prophylactic effect. In December 2014, a treatment with 300 mg of omalizumab was begun. A second dose was prescribed in January 2015, and in April 2016, no more swellings had occurred.

Discussion

InH-AAE represents a rare disease that accounts for 10 % of AAE cases in an Italian survey of 1058 patients [7]. It has been suggested that bradykinin might be involved in InH-AAE but the underlying pathophysiology remains unknown [6]. In France, tranexamic acid is the most widely used medication in these patients [17, 18]. However, its potential efficiency in InH-AAE does not necessarily reflect a bradykinergic mechanism since symptoms of CSU/CIU may also be improved

Table 1 Clinical characteristics and treatment modalities in the literature review of patients suffering from idiopathic non-histaminergic angioedema treated with omalizumab

Cases	Authors	Year	Age, sex (M, F)	Location of attacks	Total IgE level (kU/l)	Antihistamines, daily dose before OMZ, other treatments	Frequency of attacks before OMZ	Frequency of attacks on OMZ, duration of follow-up	OMZ initial dose, interval	OMZ maintenance dose, interval
1	Sands et al. [16]	2007	63, M	Tongue, larynx, and lips	62.4	Fexofenadine + cetirizine + ranitidine Corticosteroids	–	0 7 months	375 mg 2 weeks	375 mg 2 weeks
2	Von Websky et al. [21]	2013	68, M	Head and neck	1164	Ebastine, fexofenadine, desloratadine fourfold dose Corticosteroids Montelukast	–	0 >13 months	300 mg 4 weeks	300 mg 8 weeks
3	Ozturk et al. [15]	2014	47, M	Tongue, larynx, and lips	183	Anti-H1 fourfold dose	8/month	0 4 months	300 mg 4 weeks	300 mg 4 weeks
4	Azofra et al. [14]	2015	5 men 3 women	–	Mean: 121 Range: 44–402	Anti-H1 fourfold dose TA (two patients)	–	0	300 mg 4 weeks	150 mg 4 weeks
5				–			–	0	75 mg 4 weeks	75 mg 4 weeks
6				–			–	0	75 mg 3 weeks	75 mg 3 weeks
7				–			–	0	150 mg 8 weeks	150 mg 8 weeks
8				–			–	0	150 mg 8 weeks	150 mg 8 weeks
9				–			–	0	150 mg 16 weeks	150 mg 16 weeks
10				–			–	0	150 mg 8 weeks	150 mg 8 weeks
11				–			–	0	300 mg 12 weeks	300 mg 12 weeks
12	Muñoz et al. [22]	2015	55, M	Tongue, lips, and face	Range: 150–875	Anti-H1 fourfold dose, Corticosteroids, TA (2 g/day)	–	0 36 months	375 mg 2 weeks	375 mg 4 weeks
13		36, F		Tongue, lips, and face		Anti-H1 fourfold dose Corticosteroids, TA (2 g/day)	–	0 36 months	375 mg 2 weeks	375 mg 4 weeks
14	This series	2016	35, F	Tongue, lips, and face	127	Anti-H1 fourfold dose Corticosteroids	>6/month	0 12 months	300 mg 2 weeks	300 mg 2 weeks
15		88, F		Tongue, lips, face, and upper and lower limbs	58	Montelukast Anti-H1 fourfold dose Corticosteroids	>4/month	0 3 months	300 mg, 2 weeks	300 mg 2 weeks

Table 1 (continued)

Cases	Authors	Year	Age, sex (M, F)	Location of attacks	Total IgE level (kU/l)	Antihistamines, daily dose before OMZ, other treatments	Frequency of attacks before OMZ	Frequency of attacks on OMZ, duration of follow-up	OMZ initial dose, interval	OMZ maintenance dose, interval
16			49, M	Tongue, lips, face, EGO	149	Anti-H1 fourfold dose Corticosteroids Montelukast	>8/month	0 48 months	300 mg, 3 weeks	300 mg, 3 weeks
17			46, M	Tongue, larynx, lips, and face	–	Anti-H1 fourfold dose	>20/month	0 21 months	150 mg, 2 weeks	300 mg 4 weeks
18			39, M	Tongue, larynx, face, upper and lower limbs, and EGO	299	Levocetirizine, desloratadine fourfold dose Corticosteroids TA	0.5–1/month	0 –	300 mg 5 weeks	Stopped after two injections

Anti-H1/H1 antihistamines, EGO external genital organs, IgE Immunoglobulin E, OMZ omalizumab, TA tranexamic acid

upon TA [19, 20]. As in resistant forms of CSU/CIU, it may be assumed that some cases of recurrent AE non-responding to antihistamines are still “mastocyte-mediated” and may be efficiently treated with third-line therapies such as omalizumab. In clinical practice, short durations of attacks and good responses to corticosteroids argue in favor of a mast cell-mediated disease rather than a bradykinin-mediated AE. Thus, several cases of dramatic response to omalizumab in chronic antihistamine-resistant AE have been reported. Our literature review identified 13 additional cases of InH-AAE treated with omalizumab (Table 1). We notice a predominance of men (12 out of 18 patients, 67 %) and a high prevalence of upper airway involvement (9 out of 10 patients, 90 %). The threatening locations of attacks and the failure of other therapeutic options probably explain the choice of omalizumab in these patients. Interestingly, a recent study found that men suffering from IH-AAE were more likely to have an upper airway involvement than women, which may account for the preponderance of men in this review [23]. Among the five patients of this review, two had exhibited a partial improvement of their symptoms upon tranexamic acid, as described in previous studies on InH-AAE [14, 17, 18, 22].

In 6 out of 18 patients, the initial dose of omalizumab used to achieve remission was higher than the recommended schedule for CSU/CIU (300 mg monthly) [8]. In our series, the treatment interval had to be shortened in three patients because of the recurrence of AE attacks. Thus, an initial schedule of 300 mg each other week may be necessary to achieve control of symptoms.

In our experience, patients suffering from AE in the context of CSU/CIU with early relapses may benefit from a transient shortening of treatment intervals. However, this approach has still to be validated. The pharmacological mechanisms underlying these early relapses are not clearly elucidated. Thus, it is unknown whether they are related to an exacerbation of the disease or an alteration of the pharmacokinetics of the drug. By contrast, in 12 out of 18 patients, it was secondarily possible to taper the doses of omalizumab, either by progressively increasing the interval between injections (6 patients) and/or by reducing the dose (7 out of 8 patients in the series of Azofra et al.). Corticosteroids were stopped in all patients, helping to reduce their long-term side effects. Finally, no serious or unexpected adverse events related to omalizumab were reported in these case series.

The pathophysiology of InH-AAE remains unclear. As in CSU/CIU, it could be suggested to perform the autologous serum-skin test (ASST) in InH-AAE patients [8]. A positive ASST might then suggest the involvement of mast cell activation in the pathogenesis of the disease, and support the therapeutic option of omalizumab.

The exact mechanism of action of omalizumab in CSU/CIU and AE remains also poorly understood. Omalizumab, by targeting IgE and its interactions with its Fc receptor, may

increase the release threshold of mast cells [24]. IgE-FcεRI engagement may also have a role in potentiating the ability of mast cells to synthesize de novo eicosanoid inflammatory mediators and cytokines, which are involved in CSU/CIU and AE [25].

Prospective trials would be necessary to confirm the efficacy and tolerance of omalizumab and also in order to develop more suitable regimens for InH-AAE patients.

Conclusion

InH-AAE is an antihistamine-resistant form of AE whose pathophysiology remains unknown, and probably heterogeneous. Several cases of patients successfully treated with omalizumab have been reported, with a dramatic response, arguing in these cases for a mast cell-mediated disease. When initiating the treatment, higher doses than recommended for CSU/CIU may be required. The efficacy and safety profile of omalizumab in this indication are yet to be determined.

Compliance with Ethical Standards

Conflict of Interest Dr Aurélie Du Thanh, Dr Catherine Mansard, Dr Isabelle Boccon-Gibod, and Pr Laurence Bouillet have received financial support from Novartis, France.

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