



Letter

Benefits of hydroxychloroquine in the treatment of a patient with angioedema due to acquired C1 inhibitor deficiency

Autoantibody-mediated acquired C1 inhibitor (C1-inh) deficiency is a rare disorder.¹ Treatment should target both the cause and symptoms. No effective treatment for this type of angioedema has been found, other than treating the cause.²

We report on the case of a female patient, who at the age of 66 years presented with angioedema due to a functional C1-inh deficiency secondary to autoantibody production. Treatment with hydroxychloroquine in combination with tranexamic acid resolved all symptoms. We suggest that this regimen be used for this type of patient, although a randomized, double-blind evaluation is needed.

Symptoms began on August 7, 2006, with abdominal pain, vomiting of bile, and sensitivity of the right iliac fossa that lasted 2 weeks, with diagnosis of an ovarian cyst. Recurrence occurred 5 weeks later, with an attack of abdominal pain, justifying a right adnexectomy. Three months later, a swollen lip followed by a swollen left ear occurred, which resolved within 4 days. The patient noted the recurrence of abdominal pain 7 months later and facial edema with abdominal pain 8 months later.

Responsiveness to conventional treatments of edema, such as antihistamines and a short course of systemic corticosteroids, was not observed. Epinephrine was not tried. The physician in charge of this patient then transferred her to our unit.

Workup was performed on diagnosis and etiology. No angiotensin-converting enzyme inhibitors, estrogens, β -blockers, or angiotensin receptor antagonists were noted. The diagnosis of type II acquired angioedema (Table 1) was made on normal plasma concentration of C1-inh together with reduction in its functional activity and with an anti-C1-inh autoantibody. High spontaneous amidase activity (Table 1) with normal kininase activity was noted.

Extensive laboratory investigations, including anti-DNA antibodies, were then performed to search for autoimmune and hematologic

disease; all results were negative. A blood disorder was eliminated after examination of lymphocyte populations and osteomedullary biopsy; full-body computed tomography and positron emission tomography revealed the same findings for neoplasia.

Triggering conditions were unknown, with both abdominal and otorhinolaryngologic attacks occurring spontaneously.

Initiation of oral tranexamic acid therapy (3 g/d) administered 3 times daily since September 24, 2007, was followed by a lower attack frequency and decreased severity but no complete resolution. Laboratory values remained unchanged (Table 1).

After the etiologic workup, despite lack of evidence of clinical autoimmune disease, and because of biological autoimmunity demonstrated by the presence of the anti-C1-inh antibody, hydroxychloroquine was added to the regimen on May 16, 2009, with its plasma concentration measured (Table 1).

Angioedema attacks fully resolved within 2 months after hydroxychloroquine application. Clinical follow-up for 6 years was free of any attack. No modification of C1-inh was noted, in particular persistence of the anti-C1-inh autoantibody titers at the same level (Table 1). We did not find any disease occurrence (eg, autoimmune or hematologic during this follow-up).

A cautious attempt was made to taper to the minimum effective dose of tranexamic acid due to the patient's anxiety. The dosage of 2 g/d for long-term treatment, still associated with hydroxychloroquine, resulted in the rapid recurrence of the symptoms. After a first attack, the patient returned to using 3 g/d of tranexamic acid in combination with hydroxychloroquine. The effective treatment combines tranexamic acid (3 g/d) and hydroxychloroquine (400 mg/d). On an annual ophthalmologic checkup and biannual measurement of plasma concentration, within the optimal limits, no adverse effects of hydroxychloroquine already reported were noted.

Table 1
Biological data before and during treatment applications^a

Treatment	Jan 2007	Aug 2007	Mar 2009	Apr 2009	Nov 2009	Mar 2010	Jul 2010	Jan 2011	May 2011	May 2013
C1-inh antigen, mg/L (range, 210–345 mg/L)	222	129	181	121	112	139	229	119	186	69
C1-inh function, U/mL (range, 17.2–27.4 U/mL)	7.0	3.6	3.3	3.7	<2	5.9	13.0	3.8	7.0	4.4
C1-inh-specific function, U/mg (range, 67.4–93.6 U/mg)	31.5	27.8	18.3	31.0		42.2	56.9	31.9	37.6	63.8
Anti-C1-inh IgG autoantibodies, U (range, <100 U)	660	450	800	693	599	603	586	660	1,103	840
Spontaneous amidase activity, nmol/mL/min (range, 1.4–7.2 nmol/mL/min)		279.1					27.1	174.8	35.9	30.6
Proenzyme activity, nmol/mL/min (range, 1,870–2,985 nmol/mL/min)		551					3,001	1,303	2,079	2,370

^aTreatment applications were as follows: administration of tranexamic acid (3 g/d) in September 2007 and administration of hydroxychloroquine (200 mg/d) with monitoring of plasma levels in May 2009.

Disclosures: Authors have nothing to disclose.

<http://dx.doi.org/10.1016/j.anai.2014.10.008>

1081-1206/© 2014 American College of Allergy, Asthma & Immunology. Published by Elsevier Inc. All rights reserved.

The workup we present was performed at the onset of symptoms and at a 3-year follow-up, except for the osteomedullary biopsy with negative results on initial visit.

Type II acquired angioedema associated with antibody-mediated C1-inh deficiency is rare and usually associated with lymphoid hemopathies or cancer. In our study, despite an exhaustive and repeated laboratory workup, none of these diseases were found. We suggest the diagnosis of idiopathic type II acquired angioedema associated with anti-C1-inh antibodies.

The introduction of tranexamic acid was reasonable because of the observed high spontaneous amidase activity associated with the development of kinin forming proteases³ and consumption of C1-inh detected by a low C1-inh-specific function (Table 1). Icatibant and ecallantide were not available in our country in 2007. Because of a lack of clinical verification after the initially negative etiologic workup results, an attempt was made to suppress the autoimmune process of the anti-C1-inh autoantibodies. The selected therapeutic option was the same as for systemic lupus erythematosus, the most common autoimmune disease⁴ although not the diagnosis in this patient, and especially because systemic lupus erythematosus is the autoimmune disease most frequently associated with this type of autoantibody.

The choice of hydroxychloroquine was therefore warranted because of its risk-benefit ratio, despite the lack of published data, especially compared with rituximab. Rituximab was not chosen because of its doubtful efficacy and its cost.

The clinical improvement was immediate, with rapid and complete resolution of angioedema. On the other hand, the conserved titer of the anti-C1-inh antibodies remain unexplained. In addition, both C1-inh function and spontaneous amidase activity remain unchanged (Table 1).³

This implies that hydroxychloroquine did not regulate the autoantibody production. In systemic lupus erythematosus, hydroxychloroquine has been found to inhibit phagosome function, thereby preventing Toll-like receptor activation, interferon α production, and autoantigen presentation. We did not investigate these parameters in our patient.

The remaining anti-C1-inh autoantibody in a context of improved clinical phenotype is consistent with its nonimplication in the occurrence of the disease. C1-inh function and amidase activity stayed within pathological values, whereas the clinical manifestations resolved entirely. The decrease of the anti-C-inh

titer and the return to normal of biological parameters should not be an end point of the therapeutic option. An hypothesis was therefore made concerning the prominent role of high kinin formation capacity in the clinical expression of this type of edema.

This clinical effect was maintained for 6 years. The results of the etiologic assessment performed at 3 years remained negative with regard to clinical and laboratory results. There was also no need for subsequent osteomedullary biopsy because of the clinical stability and invasive nature of the procedure.

In conclusion, we suggest using the combination of hydroxychloroquine and tranexamic acid in the treatment of angioedema associated with antibody-mediated deficiency of C1-inh before using more expensive drugs with uncertain efficacy.^{2,5}

Denis Vincent, MD, PhD*

Denise Ponard, PharmD†

Sandrine Fiorella, RD‡

Christian Drouet, MD, PhD§

*Department of Internal Medicine, Service d'Asthmologie-Allergologie-Médecine Interne, CHU de Nîmes, Nîmes, France

†Service de Biochimie, CHU de Grenoble, Grenoble, France

‡Service d'Asthmologie-Allergologie-Médecine Interne, CHU de Nîmes, Nîmes, France

§Department of Biochemistry, Université Joseph Fourier Centre de Référence des Angioedèmes & Immunogénétique HLA CHU Grenoble, Grenoble, France
denis.vincent@chu-nimes.fr

References

- [1] Yildirim-Toruner C, Diamond B. Current and novel therapeutics in the treatment of systemic lupus erythematosus. *J Allergy Clin Immunol*. 2011;127:303–312.
- [2] Branellec A, Bouillet L, Javaud N, et al. French National Reference Center for Angioedema (CREAK). Acquired C1-inhibitor deficiency: 7 patients treated with rituximab. *J Clin Immunol*. 2012;32:936–941.
- [3] Defendi F, Charignon D, Ghannam A, et al. Enzymatic assays for the diagnosis of bradykinin-dependent angioedema. *PLoS One*. 2013;8:e70140.
- [4] Costedoat-Chalumeau N, Amoura Z, Hulot JS, et al. Low blood concentration of hydroxychloroquine is a marker for and predictor of disease exacerbations in patients with systemic lupus erythematosus. *Arthritis Rheum*. 2006;54:3284–3290.
- [5] Hassan A, Amarger S, Tridon A, Ponard D, Souteyrand P, D'Incan M. Acquired angioedema responding to rituximab. *Acta Derm Venereol*. 2011;91:733–734.