Eur Ann Allergy Clin Immunol Vol 49, N 2, 88-91, 2017

E. Iemoli, F. Niero, L. Borgonovo, M.V. Cossu, S. Piconi

Successful Omalizumab treatment in HIV positive patient with chronic spontaneous urticaria: a case report

Allergy and Clinical Immunology and 1st Division of Infectious Diseases, ASST Fatebenefratelli Sacco, Milano, Italy

Key words

Omalizumab; chronic spontaneous urticaria; HIV-positive

Corresponding author
Borgonovo Linda
ASST Fatebenefratelli Sacco
Milano, Italy
E-mail: linda.borgonovo@gmail.com

Summary

We described a case of a 56 year old homosexual HIV positive man who presented a history of CSU since one year (2012). All the allergologic, immunologic and microbiologic tests to evaluate the pathogenesis of wheals resulted negative. Therefore in June 2015 we decided to start therapy with Omalizumab while the patient kept on effective antiretroviral therapy with 310 cells/mm3 TCD4 counts and undetectable HIV viremia. After two monthly subcutaneous injection of 150 mg of Omalizumab the patient had no more urticarial symptoms. UAS7 (Urticaria Activity Score over 7 days) and Cu-Q2oL (chronic urticarial quality of life questionnaire) dropped respectively to 14 from 42 and to 0 from 40 with increase of TCD4 counts while viral load remained undetectable. In November 2015, i.e. 4 months after the end of Omalizumab therapy, the patient was still asymptomatic with persistent effective immune-virological response to antiretroviral therapy. This case report confirms the excellent tolerability and efficacy of anti-IgE therapy in the treatment of spontaneous chronic urticarial even in an immunodepressed patient for HIV infection. Omalizumab therapy shows a remarkable clinical success and had no effect on peripheral TCD4 counts and HIV viral load.

Chronic spontaneous urticaria (CSU), defined as episodic or daily hives lasting for 6 weeks, is a common skin condition that affects 1-3% of people in western countries (1-3) and can cause severe handicap and impairment of quality of life (4,5).

The pathogenesis of CSU is unknown, even if an autoimmune process has been proposed for a subset of patients (6). In particular, IgG auto antibodies to the α-subunit of the high-affinity IgE receptor (FcεRI) (7,8) or naturally occurring IgG anti-IgE autoantibodies (9) have been described in approximately the 35-40% and 5-10% of CSU patients respectively. Although the real pathogenetic role of these auto antibodies remains controversial, they are thought to participate in the pathogenesis by directly activating skin mast cells degranulation in a complement-dependent manner that generates urticaria (10).

Further investigation has shown that circulating basopenia, their altered IgE receptor-mediated degranulation (11), activation of coagulation and fibrinolysis cascade (prothrombin fragment F1+F2, activated factor VII and D-dimer) (12,13) in addiction to inflammatory biomarkers (IL-6 and PCR) (14,15) characterize severe disease exacerbations in CSU.

The real incidence of CSU in HIV infected patients is not known, although it should be similar to the general population. Acute urticaria has been reported as initial manifestation of human immunodeficiency virus (HIV) infection (16,17).

In HIV infection, increased serum IgE levels is associated with an expression of an imbalance between a Th1 and Th2 cytokine profile (18) and an abnormal T cell regulation of antibody synthesis by B cells. Elevated IgE levels during HIV infection is also been correlated to disease progression with advanced HIV diseases and lower peripheral TCD4+ T cells counts (19-21).

The urticaria therapeutic approach in HIV positive patients is similar to that of immune-competent patients, but from the pharmacokinetic point of view, some medications used in the

treatment of urticaria, such as steroids or cyclosporine, may cause clinical significant drug interactions with antiretroviral.
Omalizumab is a humanized murine anti-IgE antibody that has proven to be effective in the treatment of recalcitrant chronic urticaria (22,23) and it has been recommended in EAACI/WAO guidelines as add-on treatment for CSU in patients with inadequate response to H1-antihistamines (24,25).
Omalizumab, by virtue of its ability to deplete IgE, attenuates the multiple effects of IgE to maintain and enhances mast cell activities. Therefore, it reduces the ability of mast cells to release inflammatory mediators in CSU (26).
So far, in the literature there are no data about the effects of Omalizumab therapy in the HIV-positive population, although there are numerous examples of the effectiveness and lack of toxicity of the use of other biological therapy, generally speaking (27).
We describe a case of a 56 year old homosexual male. He presented a history of CSU since 2012, clinically diagnosed by two allergists in two different hospitals, with various accesses to emergency room for acute worsening. Skin prick tests for food allergens resulted negative, and no history of urticaria induced by cholinergic factors, heat, cold, water, sun and vibration emerged from the anamnesis.
He had previously been treated with short course of steroids (Prednisone, Triamcinolone and Methylprendisolone) and antihistamines (Cetirizine and Rupatadine) with only temporary resolution of wheals but subsequent recurrence of hives. In August 2013 he was hospitalized in our Department for pneumonia and latent syphilis infection. He was treated with Ceftriaxone plus Azithromycin with complete pneumonia resolution. Simultaneously latent syphilis infection was treated with diaminocillin intramuscular with subsequent RPR (Rapid Plasma Reagin) antigen negativity. HIV test was performed and resulted positive. The peripheral TCD4+ count was 113 cell/mm^3 (4%) and viral load (VL) was 90,110 copies/ml. In September 2013 he started antiretroviral therapy (HAART) with Tenofovir / Emtricitabine, Darunavir / Ritonavir, simplified in August 2014 with Epivir plus Darunavir / Ritonavir. Immunological and virological examination in February 2015 showed TCD4 299 cell/mm^3 (11.3%) and VL undetectable (< 37 copies/ml). Despite the use of antihistamine (up to four-fold) and steroids, the urticaria persisted and the patient came to our Immunological and Allergological Department. The blood tests resulted normal, except for the presence of weak positivity for ANA (1:160 speckled) and a MGUS (0.370 mg/dl) that were evaluated as non-specific results. The parasitological examinations of stools and serology for hepatitis B, A and C were negative, and total IgE were 761 KUI. The patient has been studied in another hospital with food skin prick test (negative). No intake of NSAIDs or other drugs was reported. Helicobacter pylori and thyroid autoimmunity screening resulted negative. The (Urticaria Activity Score over 7 days) UAS7 resulted 42, and (chronic urticaria quality of life questionnaire) Cu-Q2oL was 49. In June 2015, after we had obtained an informed written consent, Omalizumab 150 mg was administered subcutaneously and monthly. After only two monthly injections of Omalizumab the patient had no more urticaria symptoms and all the therapy for the treatment of urticaria was stopped. The UAS7 became 14 and the Cu-Q2oL 0, and these parameters remained stable several months later (**table 1**). During Omalizumab therapy the patient kept on antiretroviral therapy with Epivir and Darunavir / Ritonavir, and at the end of anti-IgE therapy the peripheral TCD4 count showed 326 (13.2%) cells/mm^3 and VL remained undetectable.

Table 1

Date	VL copies/ml	TCD4 cell count	TCD4 cell %	UAS7	Cu-Q2oL	Comment
August 2013	90.110	113	4%	NA	NA	start HAART[1]
February 2015	< 37	299	11%	42	49	keep on HAART[2]
June 2015	< 37	310	10.5%	42	49	keep on HAART[2] start Omalizumab
July 2015	< 37	326	13.2%	14	0	keep on HAART[2] stop Omalizumab
November 2015	< 37	307	13.4%	14	0	keep on HAART[2]

VL: viral load; TCD4: T limphocytes CD4+; UAS7: Urticaria Activity Score over 7 days; CuQ2oL: chronic urticaria quality of life questionnaire; HAART: antiretroviral therapy.
[1]Tenofovir / Emtricitabine (245/200 mg) + Darunavir / Ritonavir (800/100 mg);
[2]Epivir (300 mg) + Darunavir / Ritonavir (800/100 mg): NA: not available

In November 2015 (4 months after the end of anti-IgE therapy) the patient remained asymptomatic with persistent immuno-virological response and complete healing of wheals after only two injections of Omalizumab.

The two most important concerns for the potential use of Omalizumab in HIV positive patients are the lack of information on the response to therapy and the potential effect on viral replication and decline on TCD4+ counts.

The findings of the current case report indicate for the first time that Omalizumab could be safely and rapidly effective in the treatment of chronic spontaneous urticaria in HAART treated virologically-suppressed HIV seropositive patients.

In particular, during and after Omalizumab treatment the viral load remained undetectable and the TCD4+ cells counts kept improving (see **table 1**). The rapid and effective response of hives to a short course of Omalizumab therapy is a very particular aspect of this case report. It could give a role to antiretroviral therapy in the improvement of urticaria, but this seems unlikely due to the persistence of wheals despite two years of virologically effective antiviral therapy (from September 2013 until June 2015). Skin and mucosal tissue disorders are common during HIV infection (28) and several HIV products like gp 120, gp 41, Tat, and Nef induce human basophil chemotaxis with chemokine receptors such as CCR3 and CXCR4 (29-32). Moreover, a population of basophil / mast cell precursors in peripheral blood of allergic donors can be infected in vitro by HIV-1, and patients with AIDS have HIV-1 infected basophil / mast cell precursors in their peripheral blood (33). However, the roles of basophils in the development of HIV-related skin disorders and/or diseases progression have yet to be established in vivo. Whereas that elevated IgE concentration is a marker of Th2 activation and is associated with HIV disease progression, we could hypothesize that Omalizumab reducing IgE pool in the immune system could also play a role in improving immune function during HIV disease.

In conclusion this case report, confirming the excellent tolerability of anti-IgE therapy, showed that Omalizumab in HIV antiretroviral successful treated people should be administered in safety without modification of viral load and peripheral TCD4+ cells. However, the safety and the immunological efficacy of treatment with Omalizumab in HIV infection need further randomized controlled trials.

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