

Cholinergic Urticaria, an Effective and Safe “Off Label” Use of Dupilumab: A Case Report with Literature Review

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Abstract: Cholinergic Urticaria (CholU) is a form of generalized urticaria induced by an increase in core body temperature that activates the sweat reflex. Clinically it is characterized by localized and highly itchy wheals with surrounding erythema and can occur in response to exercise, hot baths and/or emotional stress. Dupilumab is a fully human monoclonal antibody specifically designed to simultaneously inhibit the activity of interleukin-4 (IL-4) and interleukin-13 (IL-13), which play a key role in the inflammation cascade of type 2. We report the case of a 26-year-old man suffering from CholU for 3 years, unresponsive to standard treatment in which off-label therapy was undertaken with Dupilumab, 600 mg subcutaneous as a loading dose and then 300 mg every 15 days. The daily Visual Analogue Scale (VAS) score was used to assess the efficacy of the therapy. Already after the first two administrations, the patient no longer had CholU episodes and resumed regular sporting activity, with a marked improvement in the quality of life. A possible mechanism of Dupilumab in reducing the manifestations of CholU is the blocking of the IL-4 pathway and the expression of the high-affinity IgE receptor (FcεR1) on B cells, mast cells (MCs) and basophils. By decreasing the production of FcεR1, the adhesion of IgE to the surface of MCs decreases with consequent reduction of MCs activation and histamine release. Further experience and large-scale studies may be needed to establish whether Dupilumab can be a therapeutic alternative in CholU, especially in patients who do not respond to standard treatment.

Keywords: Dupilumab, Cholinergic Urticaria, atopic dermatitis, interleukin-4, interleukin-13, acetylcholine, CholU, AD

Introduction

Cholinergic Urticaria (CholU) is a subtype of chronic inducible urticaria caused by an increase in the core body temperature, such as to activate the sweating reflex.¹ It can occur in response to physical exercise, hot bathing and/or emotional stress. Clinically it appears as pinpointing and highly pruritic wheals with surrounding erythema.^{2,3} The CholU can be accompanied by severe symptoms such as angioedema, respiratory symptoms or anaphylaxis. The diagnosis of CholU, according to the European Guidelines for CholU⁴ is based on provocation tests with physical exercise (e.g., on a treadmill or stationary bike) to be carried out up to the point of sweating which usually occurs after 10–15 minutes of exercise and then continued running for an additional 15 minutes. The test result is generally considered positive if the typical rash appears within 10 minutes from starting sweating. If positive, at least 24 hours later, a passive warm-up test with a full bath at 42°C should be performed for up to 15 minutes to rule out induced anaphylactic exercise. The current EAACI/GA2LEN/EDF/UNEV consensus recommended, as the best approach for CholU, H1 antihistamines and updosings in non-responders, along with avoidance of the trigger. In refractory cases, Omalizumab, a recombinant humanized IgG1 monoclonal antibody that binds to IgE can be considered.^{5–10} Therapeutic variations including addition of an H2 receptor antagonist, Montelukast, Scopolamine,¹¹ Danazol,^{12,13} β₂-adrenergic stimulants,¹⁴ β₂-adrenergic blockers¹⁵ and Botulinum toxin injection has been reported as an effective treatment. Desensitization therapy involving regular physical

exercise or treatment with autologous sweat may become a choice of treatment for patients with sweat hypersensitivity.^{16,17} Dupilumab is a fully human monoclonal antibody specifically designed to simultaneously inhibit the activity of two cytokines, interleukin-4 (IL-4) and interleukin 13 (IL-13), that have a key role in the cascade of inflammation type 2, at the base of numerous pathologies, such as atopic dermatitis (AD), severe asthma, nasal polyposis, eosinophilic esophagitis, prurigo nodularis and Chronic Spontaneous Urticaria (CSU). Dupilumab is currently indicated for the treatment of severe AD in children from 6 years of age, for mild-severe AD in adolescents from 12 years old and adults who are candidates for systemic therapy.¹⁸ Age-related indications for Dupilumab for AD vary from country to country. Another indication is in adults and adolescents over 12 years old as add-on maintenance treatment for severe asthma with type 2 inflammation, characterized by raised blood eosinophils and/or raised fraction of exhaled nitric oxide (FeNO), who are inadequately controlled with high dose ICS plus another medicinal product for maintenance treatment. Dupilumab is also indicated as an add-on therapy with intranasal corticosteroids for the treatment of adults with severe CRSwNP for whom therapy with systemic corticosteroids and/or surgery do not provide adequate disease control. Föhr et al described a case of a young 21-year-old woman with CSU with angioedema, CholU and AD treated with Omalizumab with poor results. Therefore, therapy with Dupilumab was opted achieving complete healing of AD, complete remission of CSU with angioedema and satisfactory control of cholinergic exacerbations for a follow-up period of 26 weeks.¹⁹ Based on case series reports found in literature, Dupilumab appears to be useful, effective and safe also in the treatment of CSU in patients unresponsive to treatment with H1 antihistamines, oral corticosteroids, anti-leukotrienes, Omalizumab and cyclosporine.^{5,20–22}

Case Report

We report on a case of a 26-year-old man affected by CholU for 3 years. He had no significant medical history, in particular no history of allergic rhinoconjunctivitis, asthma, AD in childhood or other allergic diseases and the patient was not taking drugs. The patient does not refer hyperhidrosis and according to the Hyperhidrosis Disease Severity Scale (HDSS) the score at the basal valuation was valuated 1.²³ Skin lesions present highly pruritic and pinpointing wheals with surrounding erythema especially in the photo-exposed regions, after physical exercise, even with low intensity



Figure 1 Pinpointing wheals in left arm.

Table I Laboratory Tests

Laboratory Tests	Value	Reference Ranges
BLOOD CELLS COUNT		
Leukocyte	$6.20 \times 10^3/\mu\text{L}$	4.00–10.00
Neutrophils	$3.33 \times 10^3/\mu\text{L}$	2.00–7.00
Lymphocytes	$2.24 \times 10^3/\mu\text{L}$	1.00–4.00
Monocytes	$0.37 \times 10^3/\mu\text{L}$	0.20–1.00
Eosinophils	$0.09 \times 10^3/\mu\text{L}$	0.02–0.50
Basophils	$0.05 \times 10^3/\mu\text{L}$	0.00–0.20
Erythrocyte	$4.83 \times 10^6/\mu\text{L}$	3.8–4.8
Platelet	$262 \times 10^3/\mu\text{L}$	150–450
Erythrocyte sedimentation rate (ESR)	8 mm	1.0–15.0
C-reactive protein (CRP)	2.3 mg/dL	0.00–5.00
KIDNEY FUNCTION		
Creatinine	0.08 mg/dL	0.5–0.9
Azotemia	34 mg/dL	10.0–50.0
LIVER FUNCTION		
Aspartate aminotransferase (AST)	25 U/L	4–32
Alanine aminotransferase (ALT)	28 U/L	4–32
COAGULATION TEST		
Prothrombin time (PT)	96%	70.0–130
	11.7 sec	10.0–14
International normalized ratio (INR)	10.3	0.80–1.30
Partial thromboplastin time (PTT)	25 sec	23
AUTOIMMUNE TESTS		
Antinuclear antibodies (ANA)	Negative	Negative
Extractable nuclear antigen (ENA) SCREENING (anti-Sm, RNP, Ro60, Ro62, SS-B, SCL-70, Jo-1)	<3.6 U/mL	<20
Anti-neutrophil cytoplasm antibodies (ANCA) directed against myeloperoxidase (MPO)	<3.20 U/mL	<20
ANCA- directed against proteinase-3 (PR3)	<2.30 U/mL	<20
Antiplatelet antibodies	Absent	Absent
Anti cardiolipin IgG antibodies	0.40 U/mL	<7
Anti cardiolipin IgM antibodies	0.20 U/mL	<7
Anti β 2-glycoprotein IgG antibodies	0.73 U/mL	<7
Anti β 2-glycoprotein IgM antibodies	5 U/mL	<7
Anti-double stranded DNA (Anti-dsDNA) antibodies	Negative	Negative

(Continued)

Table 1 (Continued).

Laboratory Tests	Value	Reference Ranges
TUMOR MARKERS		
Carcino-Embryonic Antigen (CEA)	1.48 ng/mL	0.00–4.70
Carbohydrate Antigen (CA) 19.9	19.4 U/mL	0.00–39
Alpha Fetoprotein (AFP)	2.23 IU/mL	0.5–5.50
IMMUNOGLOBULINS		
Cryoglobulin	Absent	Absent
Immunoglobulin G	1220 mg/dL	700.0–1600.0
Immunoglobulin A	325 mg/dL	70.0–400.0
Immunoglobulin M	107 mg/dl	40.0–230.0
IN VITRO ALLERGY TESTS		
Total IgE	65 IU/mL	0.00–100.00
Tryptase	4.06 µg/L	1.00–8.00
Eosinophil cationic protein (ECP)	10 µg/L	1.00–12.00
Specific IgE to <i>Dermatophagoides farinae</i>	0.01 kUA/L	0.0–0.35
Specific IgE to <i>Dermatophagoides pteronyssinus</i>	0.05 kUA/L	0.0–0.35
Specific IgE to grasses	0.20 kUA/L	0.0–0.35
Specific IgE to logliarella	0.16 kUA/L	0.0–0.35
Specific IgE to birch	0.12 kUA/L	0.0–0.35
Specific IgE to cat epithelium	0.03 kUA/L	0.0–0.35
Specific IgE to dog epithelium	0.04 kUA/L	0.0–0.35
Specific IgE to peanuts	0.19 kUA/L	0.0–0.35
Specific IgE to tomato	0.00 kUA/L	0.0–0.35
Specific IgE to soy	0.01 kUA/L	0.0–0.35
Specific IgE to strawberry	0.03 kUA/L	0.0–0.35
Specific IgE to peach	0.09 kUA/L	0.0–0.35
PARASITOLOGICAL EXAMINATION		
Parasitological feces	Negative	Negative

efforts such as climbing stairs, with a strong negative impact on the patient's quality of life considering that he practices running at non-competitive levels (Figure 1). The provocation test conducted with moderate exercise appropriate to the age and general condition of the patient was performed up to the point of sweating and lasted until the onset of symptoms with positive test (skin rash in 10 min). In the absence of treadmills in our Department, the test was conducted outdoors monitoring heart rate and at the external temperature of 21°C and under the supervision of a clinician. Laboratory analyses revealed normal blood count and biochemical profile, normal serum levels of total IgE and eosinophilic cationic protein (ECP), normal inflammation indices such as erythrocyte sedimentation rate (ESR) and C-reactive protein (CRP).



Figure 2 Absence of lesions in left arm after exercise test during therapy with Dupilumab.

Thyroid function, serum protein electrophoresis, and urinalysis were in the normal ranges. Antinuclear antibodies (ANA), anti-extractable nuclear antigens (ENA), neutrophil anti-cytoplasmic antibodies (ANCA), tumor markers, cryoglobulins and the parasitological faeces also had negative results (Table 1). Instrumental examinations, urea breath test, electrocardiogram, chest X-ray, abdominal ultrasound, did not reveal significant pathological findings. Patch test (SIDAPA) and prick tests for inhalants and food gave both negative results. In this case the disease did not respond to standard treatment (Rupatadine 10 mg and Hydroxyzine 25 mg even at four times the standard dose, Prednisone 25 mg, Montelukast 10 mg, Omalizumab 300 mg every month for six months) for ChIU. On the basis of the comforting data in literature about CSU, with the patient's informed consent and in compliance with the rules of our Institute, off-label therapy with Dupilumab was undertaken, 600 mg as a loading dose and then 300 mg every 15 days for six months. Monthly Visual Analogue Scale (VAS) score has been used to evaluate the effectiveness of the therapy with Dupilumab which values the overall disease bother. VAS score is a 10 cm scale with 0 meaning no disease bother and 10 being severely bothered by disease. The patients mark the scale at the point they feel corresponds to their disease bother, indicating the overall severity of their urticaria. After the first two administrations the patient already had no more episodes of ChIU (Figure 2). He has resumed regular sporting activity, with a marked improvement in the quality of life. The VAS score equal to 10 before therapy (T0) reached zero from the second month, remaining negative at 6 months of observation during therapy (Table 2). During Dupilumab therapy the patient needed Rupatadine 10 mg four times a day for the first fifteen days, then reduced doses until the antihistamine was eliminated after two months. The patient is continuing the treatment with regular follow-up and without any Dupilumab-induced adverse effect.

This work was conducted after receiving the patient's informed consent to participate in the study and to publish this report and images, in compliance with the ethical standards in the field and the norms established by the Internal Review Board of University of L'Aquila (comitato etico di Ateneo D.R. n. 206/2013 and D.R. n. 46/2017).

Table 2 VAS Improvement During Therapy with Dupilumab

Time(T)	T0	First Month	Second Month	Third Month	Fourth Month	Fifth Month	Sixth Month
VAS	10	6	0	0	0	0	0

Discussion

The patients with CholU could be categorized into three subtypes including CholU with sweat hypersensitivity, CholU with acquired anhidrosis and/or hypohidrosis and idiopathic CholU. Tanaka et al found that the sweat-induced release of histamine from basophils is mediated by specific IgE present in the sweat of patients with AD.²⁴ In normal hidrotic areas, acetylcholine released from nerves upon exercise is completely trapped by acetylcholine receptor of eccrine glands and normally induces sweating while in the hypohidrotic area, acetylcholine released upon exercise cannot be completely trapped and overflows to the adjacent MCs with consequent degranulation of the MCs and wheal development.^{25–30} Dupilumab inhibits the activity of IL-4 and IL-13, T2 cytokines, important regulators of itch that act as direct pruritogens or alter the sensitivity to other itch mediators. Type 2 inflammation-dominated skin diseases, including urticaria, are characterized by intense itching. In particular, in urticaria, IL-4 and IL-5 stimulate the production of IgE antibodies and subsequent binding to the Fcε receptor leading to activation and degranulation of MCs. Prolonged contact with IL-4 not only increases MCs expansion, but also phenotypically and functionally reshapes the cells. FcεRI cell surface expression, FcεRIα-specific mRNA and FcεRI-mediated histamine release are all augmented by IL-4, while histamine release elicited by the non-immunological stimulus remains unaffected. IL-4 alters human skin MCs after long-term exposure mimicking chronic disorders by strengthening mast cell (MC) numbers and intensifying processes associated with allergic inflammation. IL-4 likewise enhanced FcεRI expression and/or allergic stimulability.^{31–33} IL-31, notoriously involved in the pathogenesis of chronic urticaria (CU), in turn promotes the release of IL-4 and IL-13 in an autocrine cycle. This has led to the belief that directing treatment towards IL-31 (Nemolizumab) and thereby reduce the release of IL-4 and IL-13 from activated basophils or acting directly by blocking the latter (Dupilumab) may be effective in managing urticaria and therefore Phase II and Phase III studies are underway to test the efficacy and safety of Dupilumab in patients with CU.^{34–36} A possible mechanism for Dupilumab decreasing CholU manifestations is preventing the progression of the IL-4 pathway and the expression of FcεRI on B cells, MCs and basophils just as it happens in Adrenergic Urticaria. Reducing the production of FcεRI decreases the adhesion of IgE on the surface of MCs with consequent reduction in MCs activation and release of histamine.⁵ This is the first case in the literature of use of Dupilumab in a patient suffering only from CholU with optimal response to treatment. Further experiences and large-scale studies may be necessary in order to establish whether Dupilumab can be a valid therapeutic alternative in CholU, especially in patients who do not respond to standard treatment. However, the limit of the case is the absence of standardized provocation test due to the unavailability of a treadmill because it was not possible to control the subject's running speed. In the future, a standardized protocol for testing should be established.

Conclusion

The good response to Dupilumab after the failure of all previous traditional treatments, highlights the possibility to use this biological drug in the therapy of refractory CholU. Further and large-scale studies are useful to establish if Dupilumab represents an effective alternative to traditional therapies in these patients as well as in patients with CU.

A study is in progress to assess the efficacy and safety of Dupilumab in adult patients with CholU and we await the results with great interest.^{37,38}

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Disclosure

The authors report no conflicts of interest in this work.

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