

Omalizumab for Difficult-to-Treat Dermatological Conditions: Clinical and Immunological Features from a Retrospective Real-Life Experience

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Abstract

Background Omalizumab, a therapeutic monoclonal antibody specific for human IgE, has thus far been used as add-on therapy for moderate-to-severe allergic asthma in adults and children.

Objective The objective of this study was to test omalizumab efficacy in other conditions in which the IgE-mast cell axis is supposed to play a role.

Methods Nine patients with dermatological manifestations possibly related to activation of the IgE-mast cell axis (six chronic spontaneous urticaria and three atopic dermatitis patients) were administered off-label omalizumab because of refractoriness to standard therapy. All patients were subjected to strict clinical, laboratoristic, and imaging follow-up to monitor for possible adverse effects. In addition, to further

assess the role of omalizumab on T cells, mast cells, and eosinophils, T-cell immune polarisation as well as eosinophil cationic protein and tryptase serum levels were determined before and during omalizumab administration.

Results Therapy was effective in seven out of nine patients (six complete responses, one partial response, and two no responses). Interestingly, omalizumab appeared to induce lymphocyte polarisation toward a type 2 immune response and to be able to quench eosinophil-mediated inflammation, particularly in atopic dermatitis patients. Tryptase serum levels were generally low and remained unchanged during omalizumab treatment. Despite treatment spanning over several years in most of the patients, no adverse effects nor new ensuing medical conditions have thus far been observed (median follow-up: 42 months).

Conclusions Off-label omalizumab was safe and effective in our patients. The novel immunologic features recorded in our patients add further complexity to the mechanism of action of omalizumab.

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Key Points

Omalizumab can also be considered for refractory atopic dermatitis if total IgE levels fall within the range of neutralisation by the monoclonal antibody

Novel mechanisms of action include modulation of type 1 vs. type 2 immune responses and quenching of eosinophil-mediated inflammation

Dermatological conditions treated with omalizumab may be maintained in clinical control with very low doses, which may render this therapeutic strategy cost-effective with time

1 Introduction

Omalizumab, a therapeutic monoclonal antibody specific for human IgE, has been in use for more than a decade as add-on therapy for moderate-to-severe allergic asthma in adults and children. Omalizumab is highly effective in asthma and is generally well-tolerated [1]. Its mechanism of action basically involves neutralisation of circulating free IgE, which consequently leads to reduction of mast cell-bound IgE, down-regulation of high affinity IgE receptors (FcεRI) and, eventually, prevention of mediator release [2, 3]. Since the IgE-mast cell axis plays a role in many diseases other than asthma, it is conceivable that omalizumab may work as well in such settings. Indeed, in accordance with the single airway disease theory [4], omalizumab has also been shown to be effective in allergic rhinitis [5]. Moreover, following a number of case reports and small series describing the beneficial effects of omalizumab in chronic spontaneous urticaria [6–12], results from phase II and III multicentre, randomized, placebo-controlled trials in this condition have been recently become available [13–16]. Therefore, based on these studies, omalizumab has been granted marketing authorisation for chronic spontaneous urticaria by both the European Medicines Agency (EMA) and the US Food and Drug Administration (FDA) earlier this year, although it has yet to be prescribed for this indication in many countries, including Italy. However, since a significant proportion of chronic spontaneous urticaria patients do not apparently harbour circulating IgE with known allergen specificity and, in many cases, serum IgE in chronic spontaneous urticaria patients may be even low, a more complex mechanism of action has to be considered to explain efficacy of omalizumab in this peculiar dermatological condition. Following serum IgE neutralisation, the subsequent down-regulation of high affinity IgE receptors on mast cells has initially been claimed as the main effect conditioning efficacy of omalizumab in chronic spontaneous urticaria [17]. Moreover, since FcεRI-bound IgE has been shown to sustain proliferation and survival of mast cells as well as to decrease the mediator release threshold [18, 19], it appeared obvious that omalizumab, by depleting free IgE, could interfere with all of these effects. Recently, a further mechanism of action has been proposed, based on the observation that a proportion of chronic spontaneous urticaria patients have circulating IgE specific for such autoantigens as thyroperoxidase and dsDNA [20, 21]; by lowering free IgE, down-regulating mast cell and basophil FcεRI, and favouring sequestration of autoantigens by IgE-omalizumab immunocomplexes, omalizumab may prevent mast cell degranulation in this subset of chronic urticaria. However, despite all these insights, the mechanism of action of omalizumab has yet to be completely elucidated

[22]. Clinical observation indeed suggests additional mechanisms of action, since omalizumab has frequently displayed a very rapid onset of action [6–16], full activity well beyond the half-life of the drug and/or at suboptimal doses for IgE neutralisation, and, finally, no inhibition of mast cell degranulation in vivo [9]. It has been frequently reported that, in contrast to asthma, chronic spontaneous urticaria patients do not apparently need their omalizumab dose and administration schedule be calculated based on body weight and serum total IgE concentration [6–16].

Although beneficial effects have been reported in other conditions pathogenically characterised by proven or possible IgE involvement (i.e., atopic dermatitis, food allergy, specific immunotherapy, mastocytosis, anaphylaxis, etc.), scant evidence is currently available for other possible future indications [23, 24]. Here, we report our real-life experience with off-label omalizumab in dermatological conditions whose pathogenesis may suggest involvement of the IgE-mast cell axis, providing further clinical data on the efficacy and safety of omalizumab in these settings and adding new pieces to the complex puzzle of omalizumab mechanism of action.

2 Patients, Materials, and Methods

2.1 Patients

Since 2008, nine patients (six suffering from chronic spontaneous urticaria and three with atopic dermatitis, diagnosed according to standard criteria [25, 26]) have been subjected thus far to off-label treatment with omalizumab. All patients had unsatisfactory control of their dermatological condition with standard therapy. Characteristics of the patients are summarised in Table 1. For all patients, laboratory and instrumental parameters were monitored before starting omalizumab and every three to 6 months thereafter, as appropriate (Table 2). Complete response was defined as complete resolution of symptoms and signs of disease; partial response was defined as significant clinical improvement despite persistence of disease, using the urticaria activity score over 7 days (UAS7) [27] and the SCORAD (SCORing Atopic Dermatitis) index [26] for chronic spontaneous urticaria and atopic dermatitis, respectively; no response was considered in case of no benefit at all. All patients gave their informed consent prior to their inclusion in the study. The study was approved by the institutional ethics committee.

2.2 Flow Cytometry

Immunophenotyping and flow cytometric identification of circulating lymphocytes were performed before and during omalizumab therapy, according to standard protocols used

Table 1 Characteristics of patients

Patient	Disease	Age	Sex	Duration of disease	Total IgE (kU/L)	Concomitant atopy	Concomitant autoimmune thyroiditis	ASST/BHRA	Previous therapy	Omalizumab schedule	Time to and type of response	Current maintenance schedule	Time on active treatment (months)	Follow-up (months)
1	CU	53	F	13 years	557	Yes	No	Negative	AH, S, LTRA, C, Cy	300 mg every 2 weeks	48 h; CR	150 mg every 6 to 8 weeks	78	78
2	AD	22	M	Since infancy	10,208	Yes	No	NA	S, AH, Cy	300 mg every 2 weeks	2 weeks; PR: SCORAD index slowly declined from 50 to 30 in 4 months	Dropped out	7	76
3	CU	35	M	3 years	207	No	No	Negative	AH, S, LTRA	300 mg every 2 weeks	48 h; CR	150 mg every 8 weeks	64	64
4	AD	19	M	Since infancy	856	Yes	No	NA	S, AH, tP, tT	300 mg every 2 weeks	2 weeks; CR achieved in 4 months (initial SCORAD index: 43)	Currently tapered off with sustained complete response ^b Previously, 150 mg every 8 weeks	42	50
5	CU	50	F	5 months	114	Yes	Yes	Negative	AH, S, LTRA, C	300 mg every 4 weeks ^a	24 h; PR followed by CR	Terminated (sustained complete response)	4	41
6	CU	52	F	3 years	192	Yes	No	Negative	AH, S	300 mg every 4 weeks	2 weeks; CR	150 mg every 6 weeks	42	42
7	CU	73	F	9 months	6.3	No	Yes	Negative	AH, S, LTRA, C, Cy	150 mg every 4 weeks ^a	NR	Terminated for inefficacy	5	42
8	AD	20	F	11 years	821	Yes	No	NA	S, AH	450 mg every 2 weeks	2 weeks; 4 months to nearly complete response (SCORAD down from 46 to 13)	Unmodified (attempts at tapering resulted in relapse)	18	18
9	CU	56	F	14 years	21.7	Yes	No	Negative	AH, S, LTRA, Cy	150 mg every 4 weeks ^a	NR	Terminated for inefficacy	4	10

CU chronic urticaria, AD atopic dermatitis, ASST autologous serum skin test, BHRA basophil histamine release assay, NA not applicable, AH antihistamines, S steroids, LTRA leukotriene receptor antagonists, C cinnarizine, Cy cyclosporin, tP topical pimecrolimus, tT topical tacrolimus, CR complete response, PR partial response, NR no response

^a Escalated up to 300 mg every 2 weeks after unsatisfactory response

^b Sustained complete response: drug-free remission ≥ 6 months

Table 2 Biochemical and instrumental investigations carried out in patients administered omalizumab^a

Standard biochemical profile ^b
Complete blood count with differential
Serum protein electrophoresis
Serum immunoglobulin isotypes (IgG, IgA, IgM, IgE) and complement C3 and C4
Serum specific IgE ^{c,e}
Circulating lymphocyte subsets
Autoimmunity profile (RF, ANA, anti-dsDNA, AMA, ASMA, anti-ENA, ANCA, cryoglobulins)
Cancer markers ^d
HBsAg and HCVAb ^e
Thyroid function screening ^f
Stool examination for parasites ^{g,e}
Stool examination for <i>Helicobacter pylori</i> ^{g,e}
Urinalysis
ASST or basophil histamine release test ^{g,e}
ECG ^h
Chest X-ray ^h
Abdominal US scan ^h

RF rheumatoid factor, ANA anti-nuclear antibodies, *anti-dsDNA* anti-double stranded DNA, AMA anti-mitochondrial antibodies, ASMA anti-smooth muscle antibodies, ENA extractable nuclear antigens, ANCA anti-neutrophil cytoplasmic antibodies, HBsAg hepatitis B surface antigen, HCVAb hepatitis C virus antibodies, ASST autologous serum skin test, ECG electrocardiogram, US ultrasound, CEA carcinoembryonic antigen, α -FP α -fetoprotein, CA cancer (carbohydrate) antigen

^a Repeated every 3–6 months, unless otherwise stated

^b Includes: erythrocyte sedimentation rate, C reactive protein, electrolytes, calcium, phosphorus, glucose, urea nitrogen, creatinine, total protein, triglycerids, cholesterol, aspartate aminotransferase, alanine aminotransferase, pseudocholinesterase, γ -glutamyltranspeptidase, alkaline phosphatase, bilirubin, iron, ferritin, transferrin, uric acid, amylase, creatine kinase, lactate dehydrogenase

^c Tested allergens include those comprised in the ImmunoCAP[®] ISAC (Immuno Solid-phase Allergen Chip) microarray system (Phadia, Thermo Scientific) for the most recent patients; before availability of the multiplex ISAC test, patients were usually screened for the following allergens: house dust mite, grass pollen, wall pellitory, cypress, olive, birch, mugwort, cat and dog dander, latex, wheat, egg white, tomato, milk, soy, peanut, tree nut, apple, peach, *Anisakis simplex*

^d Include: CEA, α -FP, CA19-9, CA125, CA15-3, CA50, β_2 -microglobulin, thymidine kinase

^e Only on admission

^f Includes: thyrotropin, free thyroxine, free triiodothyronine, anti-peroxidase and anti-thyroglobulin autoantibodies

^g Only for chronic urticaria patients

^h Before starting omalizumab and at yearly intervals thereafter, if normal

in our laboratory, as previously detailed [28, 29]. All fluorochrome-conjugated monoclonal antibodies were obtained from BD Biosciences (San Diego, CA, USA), unless otherwise stated. Apart from evaluation of standard lymphocyte subsets (T, B, NK, and NK-T cells), in order to investigate whether omalizumab could affect the relative balance between Th1/Tc1 and Th2/Tc2 lymphocytes (mediators of type 1 and type 2 immune responses, respectively), immunophenotyping was also performed using very specific surface markers for the above T-cell subsets, namely CCR5 (for Th1/Tc1 cells) [30, 31] and CRTH2 (for Th2/Tc2 cells) [32–34]. To facilitate evaluation of omalizumab effects on type 1 and type 2 immune responses, the CCR5/CRTH2 ratio was used, as previously described [35, 36]; thus, an increasing CCR5/CRTH2 ratio was deemed indicative of a switch toward a predominant type 1 immune response, whereas a decreasing CCR5/

CRTH2 ratio was considered consistent with a prevailing type 2 immune response [35, 36]. The following cell membrane molecules were therefore investigated using specific fluorochrome-conjugated monoclonal antibodies: CD3, CD4, CD8, CD19, CD16, CD56, CCR5, CRTH2/CD294 (Miltenyi Biotec, Germany). Acquisition of data was carried out on a BD FACSCalibur flow cytometer (BD Biosciences); analysis of T-cell subsets was performed by gating on total CD3+ T lymphocytes using the WinMDI software version 2.9 (Joseph Trotter[®], Scripps Research Institute, La Jolla, Ca, USA).

2.3 Eosinophil Cationic Protein (ECP) and Tryptase Serum Levels

To investigate the role of omalizumab on activated eosinophils and mast cells, their main secretion products, i.e.,



Fig. 1 Representative effect of omalizumab in a chronic urticaria patient (#6). Diffuse, scattered hives (a, c), occurring daily in the 3 years prior to commencing omalizumab treatment. The patient had immediate benefit following the first injection of omalizumab; remission (b, d) was fully achieved within 2 weeks after the first administration of omalizumab

ECP and tryptase, respectively, were measured in the serum of patients before and during omalizumab treatment using the ImmunoCAP® ECP and tryptase kits on a Phadia® 250 immunoassay analyser (Thermo Scientific), according to the manufacturer's instructions.

2.4 Omalizumab Schedule

Patients were initially treated according to the schedule proposed for allergic asthma, i.e., based on body weight and total serum IgE concentrations. Omalizumab dose was increased in case of unsatisfactory response or slowly tapered off in case of remission, as previously detailed [9].

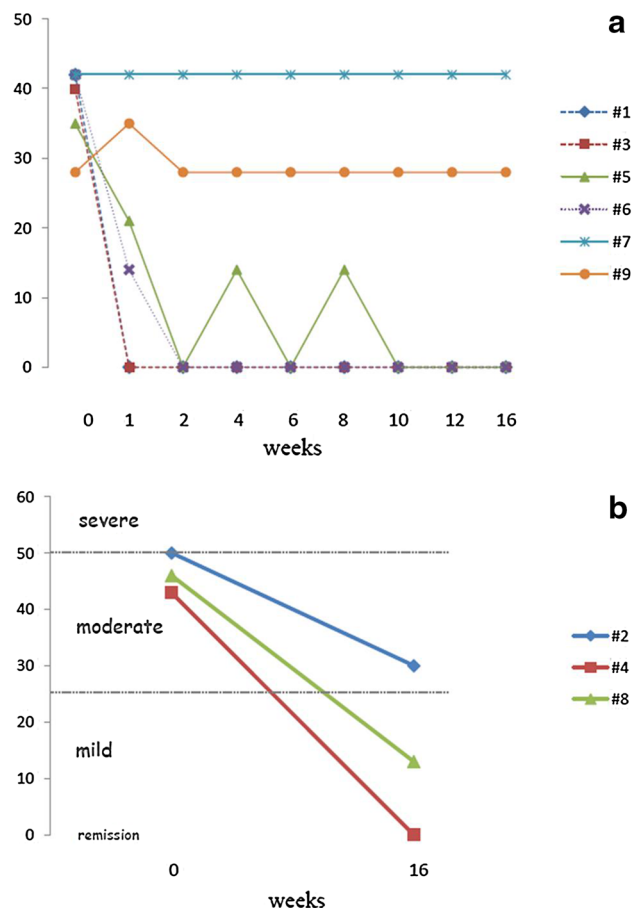


Fig. 2 Time course of UAS7 (a) and SCORAD index (b) following omalizumab treatment. See text for details

2.5 Follow-Up

Patients were subjected to laboratory investigations quarterly for the first 2 years of omalizumab therapy, then every 6 months. Patients were also subjected to imaging techniques before omalizumab treatment and at least yearly thereafter (Table 2). Clinically, the patients were evaluated on each injection day, i.e., every 2–4 weeks, depending on the individual administration schedule.

3 Results

3.1 Patients

Overall, six of nine patients had a complete response (67 %), one patient had a partial response (11 %) and two patients (22 %) did not improve at all. The rate of complete response was 67 % both in chronic spontaneous urticaria (four of six patients) and in atopic dermatitis (two of three patients). In patients with chronic spontaneous urticaria, remission was obtained within a few days up to a couple of

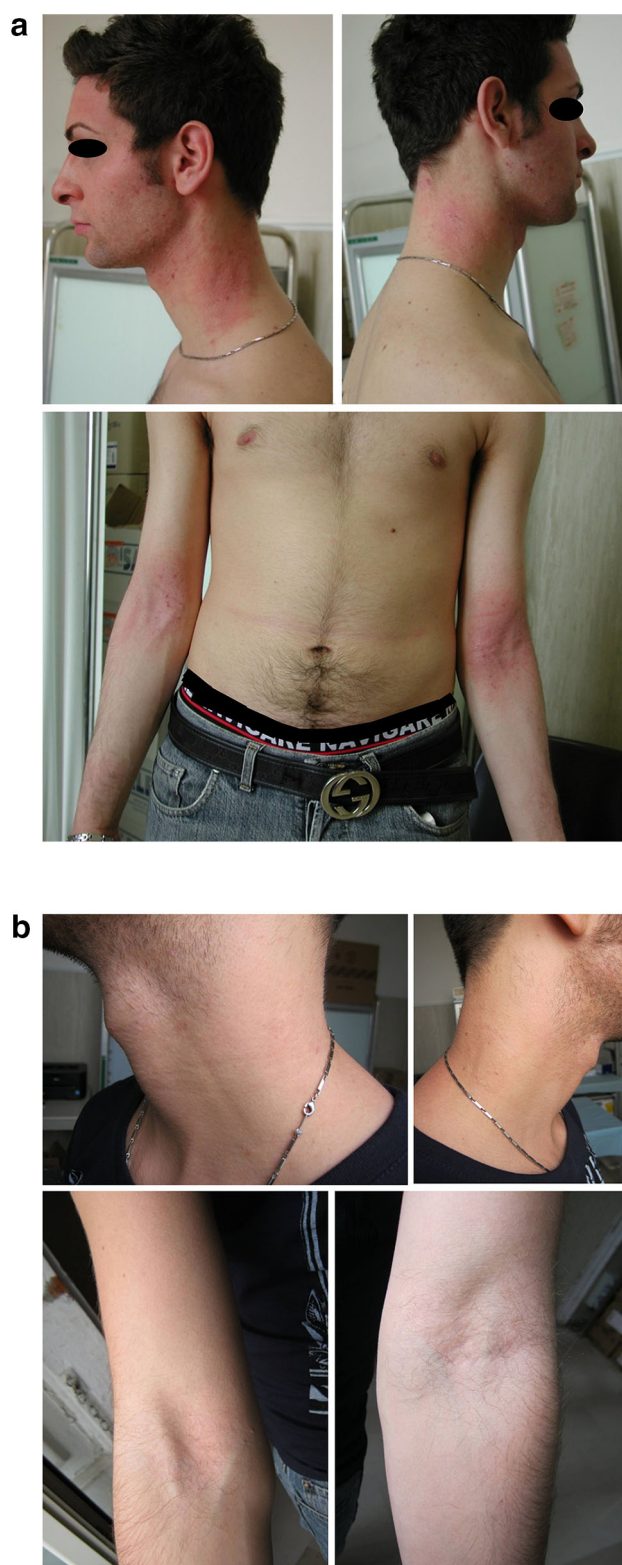


Fig. 3 Efficacy of omalizumab in atopic dermatitis. Patient #4: involvement of face, neck, and flexural regions of the upper limbs, with erythema, oedema, xerosis, excoriations, and lichenification, before initiating treatment with omalizumab (a). Four months after beginning omalizumab treatment, the patient had a complete response (b). No concomitant therapy with other systemic or topical drugs (e.g., steroids, cyclosporine, methotrexate, tacrolimus, pimecrolimus, etc.) was associated to omalizumab in this case. Complete remission was successfully maintained with low-dose omalizumab (150 mg every 6–8 weeks)

(Table 1; Fig. 1); patient #5 needed shorter administration intervals to obtain and maintain a complete response (occurrence of episodes of hives around the end of the 30-day cycle). Two patients (#7 and #9) did not respond at all to treatment with anti-IgE; interestingly, these two patients had the lowest levels of circulating IgE before starting therapy (6.3 and 21.7 kU/L, respectively, Table 1). The time course of UAS7 in chronic spontaneous urticaria patients is depicted in Fig. 2a. Among the atopic dermatitis patients (#2, 4, 8), it is noteworthy that the two patients (#4 and #8) with pre-treatment circulating IgE levels within the range of neutralisation (<1,500 kU/L, depending on body weight) by currently available doses of omalizumab, both obtained a complete response, with progressive improvement over several months (Table 1; Figs. 2b, 3). Moreover, omalizumab was the only drug used for inducing and maintaining the clinical response. Patient #2, who was on cyclosporine and whose circulating IgE levels were well above the maximum threshold for neutralisation (10,208 kU/L) by the anti-IgE, could only partially benefit from omalizumab therapy (SCORAD down from 50 to 30, Fig. 2b). Thus, in our experience, too low or too high circulating IgE levels appeared to meaningfully affect the outcome of the clinical response to omalizumab.

3.2 T Cell Polarisation

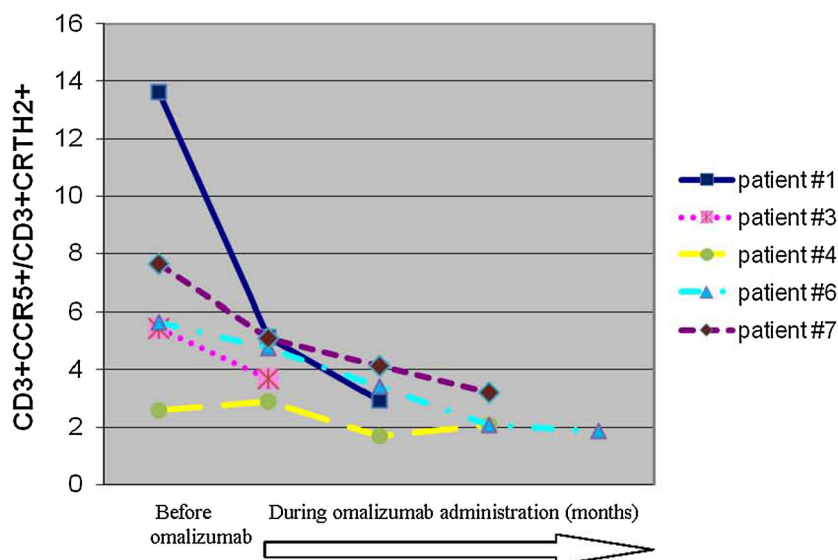
Data on the effects of omalizumab on T-cell polarisation were available for six of the nine patients. Patient #2 was excluded from analysis because of concomitant treatment with cyclosporine. Intriguingly, omalizumab determined a progressive reduction in the CCR5/CRT2 ratio in all the examined patients, suggesting polarisation toward a type 2 immune response (Fig. 4). This novel finding adds further complexity to the mechanism of action hypothesised for omalizumab, making its effects even more pleiotropic than initially predicted.

3.3 ECP and Tryptase Serum Levels

ECP serum levels were found to be more elevated in patients with atopic dermatitis than in chronic spontaneous urticaria patients (Fig. 5), probably reflecting a more significant role for eosinophils in the pathogenesis of atopic

weeks of the first drug injection, whereas atopic dermatitis patients had a progressive improvement over several weeks (Table 1). Specifically, chronic spontaneous urticaria patients #1, 3, 6 rapidly achieved a complete response

Fig. 4 Effect of omalizumab on T-cell polarisation. Omalizumab was associated with a decreasing CD3+CCR5+/CD3+CRTH2+ ratio, suggesting progressive polarization toward a type 2 immune response. This was evident at least as early as 4 weeks following initiation of omalizumab treatment and was further confirmed in the following months



dermatitis with respect to chronic spontaneous urticaria. Overall, omalizumab determined a progressive decline in ECP serum levels, which was more pronounced in atopic dermatitis patients (Fig. 5b), as discussed above. Consistently, dermatitis flares were paralleled by elevations in ECP serum levels (Figure 5b). On the contrary, tryptase serum levels ($\mu\text{g/L}$) were generally low (mean $\pm$ SD $5.53 \pm 4.07 \mu\text{g/L}$, median $4.58 \mu\text{g/L}$) before starting omalizumab and did not change during treatment (mean $\pm$ SD $5.13 \pm 3.33 \mu\text{g/L}$, median $4.71 \mu\text{g/L}$, 16th week of therapy).

3.4 Follow-Up and Adverse Effects

Mean $\pm$ SD follow-up time at the time of this report was 46.8 ± 23.4 months (median 42 months, range 10–78 months). No patients suffered from any type of infection, neither helminthic and/or parasitic. Cancer screening was negative in all patients during treatment and follow-up. No episodes of arterial thromboembolism were recorded. There was no induction of commonly searched autoantibodies. All patients reported pain at the injection site during administration.

4 Discussion

Our experience confirms the conceptual usefulness of omalizumab in diseases other than asthma where the IgE-mast cell axis may be hypothesised to play a significant role. Moreover, the brilliant results obtained in patients with chronic spontaneous urticaria implicitly demonstrate that the IgE-mast cell axis is involved in most cases of chronic urticaria. Of note, only the patients with total IgE

serum levels within the range of neutralisation with the currently available omalizumab schedules showed progressive improvement up to clinical remission; the patient (#2) with partial response had total IgE levels far beyond the neutralisation capability of full dose omalizumab; on the other hand, the worst responses in chronic spontaneous urticaria patients were observed in those subjects whose total IgE levels were very low (i.e., 6 and 23 kU/L, respectively). Atopy did not seem to “help” omalizumab do the perfect job; indeed, patient #3, who did not have apparent specific sensitisation to common allergens, had a good outcome; conversely, patient #9, who was atopic, turned out to be a nonresponder. Thus, in our experience, only pre-treatment serum total IgE levels appeared to influence the outcome, both in chronic spontaneous urticaria and atopic dermatitis patients (Table 1). Other interesting issues surfaced from our experience. First, omalizumab appeared to modify even the events upstream the IgE-mast cell axis, as the relative ratio between CRTH2+ and CCR5+ T lymphocytes, i.e., type 1 vs. type 2 T cells, was shown to be progressively modified by treatment with the anti-IgE; specifically, this novel finding suggests omalizumab-driven T-cell polarisation towards a predominant type 2 immune response. The functional significance of this effect is not clear at the moment; if Th2/Tc2 lymphocytes and IgE are in mutual balance, IgE neutralisation may therefore result in an enhanced type 2 immune polarisation, similar to what is typically observed in endocrine regulatory mechanisms [37]; alternatively, a type 2 immune response characterised by a significant secretion of the immunosuppressive cytokine IL-10, which may help dampen the inflammatory response in the skin, may be theorised to occur [38]. Finally, at least in atopic dermatitis patients, it may be hypothesised that type 1

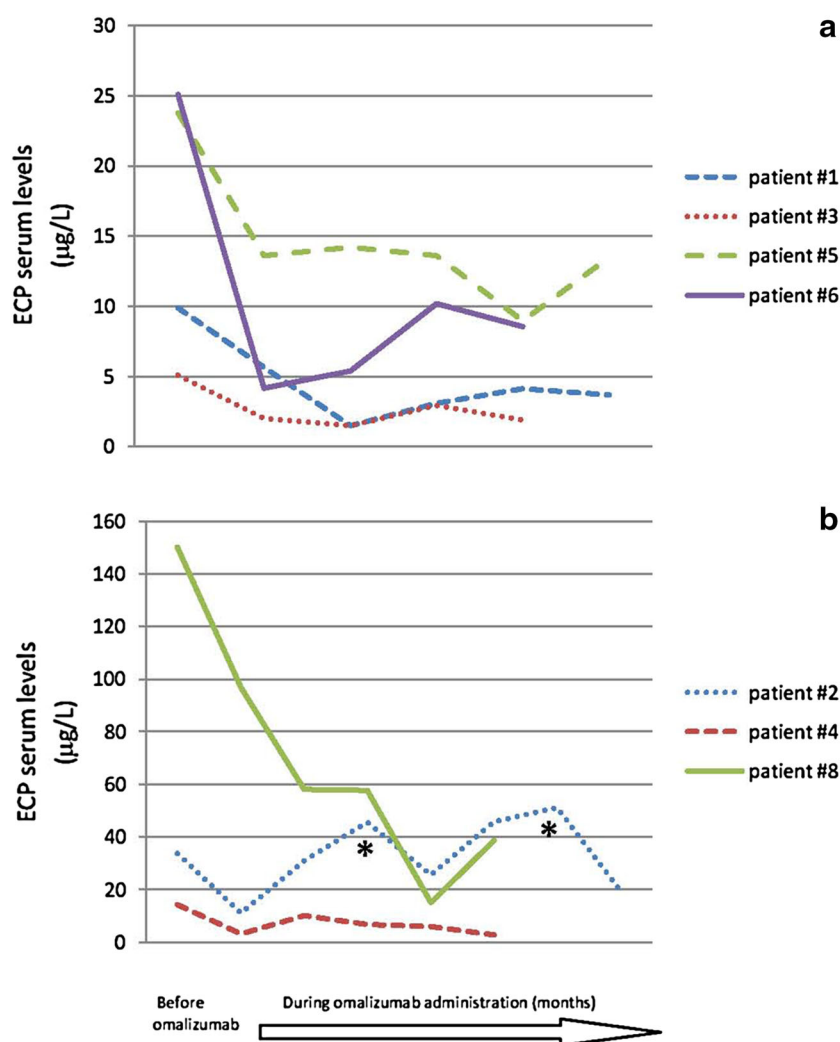


Fig. 5 Behaviour of eosinophil cationic protein (ECP) serum levels in chronic urticaria (**a**) and atopic dermatitis (**b**) patients. In all patients, omalizumab treatment was associated with a reduction in ECP serum levels. Chronic urticaria patients displayed lower levels of ECP serum levels with respect to atopic dermatitis patients before starting treatment with omalizumab, suggesting a more significant role for activated eosinophils in the latter dermatological condition. This is also inferred by the observation of rising ECP levels during episodes of dermatitis flares (*asterisks* patient #2). Interestingly,

control of dermatitis by omalizumab in patient #2 was partial and complicated by flares, probably due to the very high pre-treatment IgE serum levels (10,208 kU/L), suggesting incomplete neutralisation of free circulating IgE by omalizumab. In this patient, cyclosporine was maintained during omalizumab administration; flares were observed during attempts at reducing cyclosporine dose. Patient #4 had the lowest ECP serum levels among atopic dermatitis patients probably because of chronic steroid therapy continued up to the day before starting omalizumab

immune responses progressively subside as the skin condition improves (possibly due to reduced infection-triggered immune responses, as infectious agents are known to induce type 1 immune responses and to cause increased morbidity in atopic dermatitis patients [39]). Studies focusing on the pattern of T cell cytokine secretion are currently ongoing in order to give a better interpretation to the immune polarisation effect mediated by omalizumab.

Second, among the events occurring downstream the IgE-mast cell axis, omalizumab appeared to have a role in quenching the eosinophil-mediated inflammation. This was particularly evident in atopic dermatitis patients, where the

clinical response was paralleled by a progressive decrease in ECP levels, a marker of eosinophil activation; consistently, dermatitis flares were associated with elevations in ECP serum levels. Indeed, eosinophils are just one of the multiple players (lymphocytes, monocytes/macrophages, Langerhans cells, keratinocytes, and mast cells) involved in the pathogenesis of the complex inflammatory process underlying the clinical manifestations of atopic dermatitis [40]. Based on our results, eosinophils appear to be important participators in the inflamed skin of atopic dermatitis patients. With due differences, our observations are in accordance with the findings described by Djukanovic

et al. [41] and Riccio et al. [42], who reported a reduced eosinophil infiltration in the bronchial mucosa of allergic asthma patients following institution of omalizumab treatment. Moreover, with regard to chronic urticaria, our data appear to confirm the pathogenic role of eosinophils hypothesised by Asero et al. [43]. Although tryptase serum levels appeared unmodified in all patients treated with omalizumab, this finding does not belittle the role of mast cells as effector cells. Indeed, among the numerous medical conditions characterised by mast cell degranulation, high tryptase serum levels can generally be found only in cases of massive degranulation (anaphylaxis) or secondary to an expanded mast cell burden (mastocytosis) [44]. Thus, tryptase serum levels cannot be used to monitor mast cell activity and response to omalizumab both in chronic spontaneous urticaria and atopic dermatitis.

Third, most responder patients were maintained in complete remission with low-dose omalizumab, i.e., using suboptimal doses for fully effective total IgE neutralisation. These patients, although free from clinical manifestations, still displayed the *in vivo* mast cell response, suggesting availability of sufficient mast cell-bound IgE amenable to cross-linking by allergens on exposure (personal observations and [9]). These observations indicate that at least some of the positive effects exerted by omalizumab may be independent of circulating IgE neutralisation. The fact that our patients could be maintained in long-term remission with low-dose omalizumab may also have advantageous economic implications; in other words, the cost for maintaining these patients in remission may even turn out to be lower than the direct and indirect costs imposed on the national health agencies and governments by these ailments [45, 46], especially with the expected abatement of the costs of the monoclonal antibodies with time.

Finally, the optimal safety profile of omalizumab is to be emphasised; the feared complications—infection (particularly, parasitic and helminthic), cancer, autoimmunity induction, and/or thrombosis/vascular accidents were not observed during our long-term follow-up, with pain at the injection site being the sole complaint reported by all patients.

5 Conclusions

Omalizumab was safe and effective both in chronic spontaneous urticaria and atopic dermatitis. In our experience, pre-treatment serum IgE levels appeared to affect the outcome of the clinical response, with too high or too low concentrations associated with incomplete or no responses, respectively. Omalizumab appeared to exert novel immunologic effects, both upstream (T-cell polarisation toward a type 2 immune response) and downstream (blunting of eosinophil-mediated inflammation) the IgE-mast cell axis.

In addition, at least some of the beneficial effects induced by omalizumab may be independent of circulating IgE neutralisation. The possibility of maintaining the clinical response with very low doses of omalizumab may eventually turn out to be cost-effective, especially with the expected abatement of the costs of the monoclonal antibodies with time.

Conflict of interest No sources of funding were used for the conduct of this study. The authors declare that they have no conflict of interest.

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