

Treatment of refractory chronic urticaria with tumor necrosis factor- α inhibitors

To the Editor: Chronic urticaria is a physically and emotionally debilitating condition that often fails to respond adequately to antihistamines. Systemic therapy with glucocorticoids, sulfasalazine, colchicine, intravenous immunoglobulin, dapsone, or other immunosuppressants including cyclosporine, cyclophosphamide, and methotrexate are used in many patients with the associated risks of renal and hepatic toxicity and anemia. Unfortunately, some patients have disease recalcitrant to these treatments.

The pathogenic mechanisms of chronic urticaria are not well understood, but the primary effector cell is likely the mast cell. Activated mast cells release mediators, including tumor necrosis factor- α (TNF- α), that recruit other immune cells and play a role in perpetuating an urticarial response. TNF- α is known to exist preformed in mast cells and to be newly synthesized upon mast cell activation.¹

Several preclinical investigations have shown an upregulation of TNF- α in patients with chronic urticaria.¹⁻³ Magerl et al⁴ described a patient with severe psoriasis and delayed pressure urticaria who became free of urticarial lesions after 4 days of treatment with etanercept. Based on these preclinical investigations and the case report, we treated six of our most refractory chronic urticaria patients with TNF- α inhibitors. The choice of TNF- α was primarily based on the patient's insurance and our experience using the medications. When possible, we used doses tested for other systemic inflammatory conditions, such as psoriasis.

A brief summary of each patient's background and treatment course is provided in Table I.

The theoretical basis for the use of TNF- α -targeting therapy to treat urticaria is supported by studies that have shown the upregulation of TNF- α in chronic urticaria. In a study of 19 chronic urticaria patients and 15 healthy controls, cytokine and chemokine production after autologous serum skin testing was analyzed and TNF- α , interleukin (IL)-10, RANTES, and macrophage inflammatory protein-1 α were upregulated in chronic urticaria patients but not controls.² In another study that compared levels of TNF- α in lesional and nonlesional skin of chronic urticaria patients, TNF- α was found to be expressed throughout the epidermis in lesional and nonlesional chronic urticaria skin but not in control skin.³ Furthermore, a study by Piconi et al² revealed similar immunologic profiles in patients with chronic urticaria and with rheumatoid arthritis, psoriasis, and psoriatic arthritis, with increased expression of

TNF- α and IL-10, and decreased expression of IL-2 and interferon gamma.⁵ Interestingly, these diseases, along with chronic urticaria, tend to worsen with infection. Perhaps a common link may be an aberrant response of innate immunity mediated through TNF- α expression.

In our series of six patients who were recalcitrant to all other immunosuppressive therapies, we observed dramatic improvement with TNF- α inhibitors. In most cases, the improvement was durable, lasting for several years, and in three cases the patients were subsequently tapered off all systemic treatment and their urticaria remains in remission. These results suggest that targeted TNF- α therapy may be useful for disease refractory to conventional or immunosuppressive therapy. Larger, controlled studies with longer follow-up periods are needed to further confirm the efficacy and safety of TNF- α inhibitors in the management of patients with chronic urticaria.

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Table I. Demographic data and clinical course of the study patients

Case no.	Age (y)/gender	Disease description	Disease duration (y)	Previous treatments	Initial TNF- α inhibitor and dose	Clinical course after initiation of TNF- α inhibitor therapy
1	51/F	CIU and angioedema	20	Antihistamines, prednisone, colchicine, dapsone, cyclosporine, and mycophenolate mofetil	Etanercept 50 mg BIW	Cleared in 4 wks After 1 yr of treatment, tapered off etanercept Flared 6 months later Restarted etanercept and cleared again Tapered off etanercept again and has been clear for 2 yrs
2	52/F	CUV	1.5	Antihistamines, prednisone, colchicine, dapsone, cyclosporine, and montelukast	Etanercept 25 mg BIW	Improved within 2 months Tapered off cyclosporine and prednisone Maintained clearance on etanercept for 15 months Discontinued etanercept 7 months ago and remains clear
3	29/F	CUV	11	Antihistamines, colchicine, dapsone, cyclosporine, mycophenolate mofetil, phototherapy, and methotrexate	Etanercept 50 mg BIW	Responded well, but after 4 months had breakthrough urticaria Switched to infliximab, and urticaria cleared in 1 month Had flares and methotrexate was added (10 mg/wk) Maintained on infliximab and MTX with occasional hives
4	54/F	CUV	20	Antihistamines, dexamethasone, IM triamcinolone, colchicine, dapsone, cyclosporine, mycophenolate mofetil, methotrexate, hydroxychloroquine, azathioprine, and indomethacin	Adalimumab 40 mg QOW	After first month, lesions shorter in duration After 2 months, reported 75% improvement Cleared by 5 months Remains clear after 9 months and has been weaning off adalimumab without flares
5	35/F	CIU	12	Antihistamines, prednisone, colchicine, dapsone, cyclosporine, mycophenolate mofetil, montelukast, sulfasalazine, methotrexate, hydroxychloroquine, and IVIG	Infliximab 5 mg/kg q6 wks	At 1 month, tapered off prednisone and cyclosporine Clear for 5 months, then switched to etanercept but it did not control urticaria Cyclosporine restarted, but with no benefit Restarted infliximab with total clearance Clear for almost 3 years Over the last 6 months has started flaring before infusions The addition of cyclosporine has controlled flares
6	49/M	CIU	2	Antihistamines, prednisone, colchicine, dapsone, cyclosporine, mycophenolate mofetil, and methotrexate	Etanercept 50 mg BIW	After 1 week of treatment with etanercept, urticaria resolved completely No recurrence to date (4 months) Patient has begun tapering off etanercept now; currently on 50 mg once a week

BIW, Twice a week; CIU, chronic idiopathic urticaria; CUV, chronic urticarial vasculitis; F, female; IM, intramuscular; IVIG, intravenous immunoglobulin; M, male; q6 wks, every 6 weeks; QOW, every other week; TNF- α , tumor necrosis factor- α .