

Effectiveness of omalizumab in a case of urticarial vasculitis

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Summary

Urticarial vasculitis (UV) is a mainly leucocytoclastic vasculitis with urticarial plaques. Treating these patients is challenging as the available treatments have poor efficacy. Oral corticosteroids are considered the first-line treatment, but H1 antihistamines, dapsone, colchicine, antimalarials, ciclosporin and antileucotrienes have all been tried also. However, because of their adverse effects and/or lack of efficacy, new agents are still needed. Omalizumab, an anti-IgE antibody, shows efficacy in chronic spontaneous urticaria, and might also be a good treatment for angio-oedema and urticarial vasculitis. To our knowledge, there have been only seven relevant case reports published in the English literature. We add a new case of severe chronic recurrent urticarial vasculitis refractory to all of the drugs mentioned above. We started the patient on subcutaneous omalizumab 300 mg every 4 weeks, which produced clinical improvement within the first month and total remission in the fifth month. The patient has remained stable for 23 months, and follow-up is ongoing.

Urticarial vasculitis (UV) is a predominantly leucocytoclastic vasculitis with urticarial plaques. Oral corticosteroids are considered the first-line treatment, but carry adverse effects (AEs). Consequently, several therapeutic alternatives have been tried, including dapsone, colchicine, antimalarials and ciclosporin,^{1,2} but all have shown unsatisfying results. We report our experience using omalizumab, an anti-IgE antibody, to treat a patient with UV.

Report

A 71-year-old woman, pseudoallergic to several non-steroidal anti-inflammatory drugs, presented with a 10-year history of generalized, pruriginous, painful and occasionally burning, urticaria. Previously, both sedating and nonsedating H1 antihistamines (up to four times the standard dose) for at least 6 months

had failed. Oral prednisone (0.5 mg/kg/day) and ciclosporin (200 mg/day) had achieved remission but with early relapse after drug cessation, while montelukast (10 mg/day) and dapsone (100 mg/day) had been only minimally effective. The condition had worsened in the past 2 years (over 25 lesions per day) with occasional angio-oedema and impaired daily activities [weekly Urticaria Activity Score (UAS7) of 32 points and Chronic Urticaria Quality of Life Questionnaire (CU-Q2oL) of 62.9]. No trigger had been identified.

On physical examination, urticarial plaques were seen on the patient's back (Fig. 1) and generalized to other areas.

Autoimmune profile was positive for parietal cell autoantibodies, intrinsic factor, anti-thyroid peroxidase (anti-TPO) antibodies, antinuclear antibodies (ANAs; 1 : 100). *Helicobacter pylori* IgE was 160 U/mL (normal range < 10 U/mL).

Previous biopsies showed signs of urticaria. However, owing to the persistence of the plaques for > 24 h, a slight residual hyperpigmentation and suggestive dermoscopic signs (purpuric points and globules on a brown–orange patchy background) on the thighs, a new procedure was performed, which showed a neutrophilic infiltrate surrounding small vessels in the upper dermis, with leukocytoclasia (Fig. 2).

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Figure 1 Urticarial plaques on the upper back.

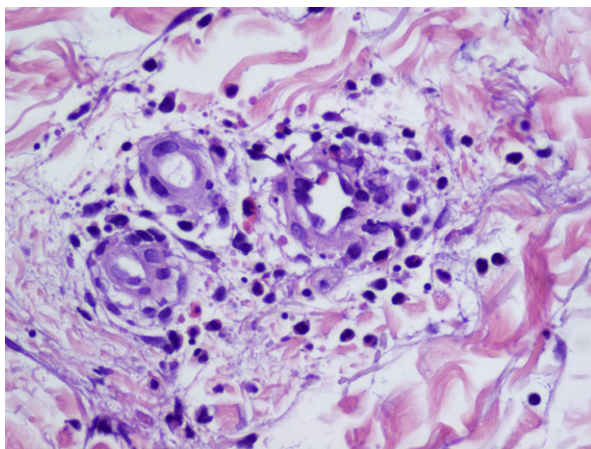


Figure 2 Neutrophilic infiltrate surrounding small vessels in the upper dermis, with leucocytoclasia (haematoxylin and eosin, original magnification $\times 40$).

The patient was diagnosed as having leucocytoclastic UV with perivascular infiltrate of neutrophils.

As mentioned above, a number of previous therapies had failed. Long-term maintenance steroid or ciclosporin therapy was not acceptable to the patient. Because omalizumab was recently reported as effective

in chronic urticaria (CU) and angio-oedema, we decided to use that because of its better safety profile. Accordingly, omalizumab 300 mg monthly was prescribed.

Although the UAS is a tool validated for CU and not UV, we used the UAS7 as a measure before the first injection of omalizumab (as mentioned, her UAS then was 32) and complete remission was achieved after the fifth dose (UAS of 0). At that time, the antihistamines were reduced to occasional intake, if needed. Both quality of life and sleep improved for the patient, as measured by CU-Q2oL. She remained stable after 12 months of omalizumab 300 mg monthly and no AEs were seen. At week 52, we lowered the omalizumab dosage to 150 mg monthly. Some weals and pruritus appeared in the next 3 months but only occasional antihistamines were needed to control these. At week 78, we tapered omalizumab to 150 mg every 6 weeks. The patient has remained asymptomatic for 23 months on this maintenance dose, and follow-up is ongoing.

UV is predominantly a small-vessel leucocytoclastic vasculitis (particularly of postcapillary venules), with weals. It may be associated with connective tissue diseases, neoplasm (lymphoma, monoclonal gammopathy), chronic infection, drugs and sun exposure.² UV may be divided into normocomplementaemic and the more severe hypocomplementaemic variant with systemic manifestations (angio-oedema, arthralgia, abdominal or thoracic pain, fever, pulmonary or renal disease, episcleritis and uveitis). Prevalence is higher among middle-aged women. Clinically, UV is characterized by the presence of weals or urticarial plaques with pain/burning sensation rather than pruritus, lasting more than 24 h and sometimes with persistent hyperpigmentation.

UV may be mediated through immune complexes, complement activation, capillary permeability and neutrophil chemotaxis upregulation. Interleukin (IL)-1 may also be involved, as similar clinical findings have been found in autoinflammatory diseases, and some patients have had reduction of UV symptoms with the use of IL-1 antagonists.

UV is difficult to treat, and several drugs have been used, including antihistamines, oral corticosteroids, cyclophosphamide, rituximab, dapsone, indomethacin and colchicine.¹⁻³

Omalizumab is an anti-IgE humanized recombinant monoclonal antibody that binds to the IgE C3 domain. It produces immunomodulatory effects beyond plasma IgE binding, including a decrease in IgE cell receptors in mast cells and basophils. It produces reductions in B-cell activation and homing. It also induces eosinophil apoptosis, increases IL-2, IL-3,

tumour necrosis factor- α and interferon- γ , and reduces IL-4.^{3–5} It may be effective in UV through its reduction of IgE and through downstream effects on cellular activation mechanisms (possibly a reduction in chemotaxis or immune complex formation).

In our case, all previous therapies had failed, and we prescribed omalizumab 300 mg monthly. With this treatment, the disease was partially controlled within 1 month, with a notable decrease in UAS7 from 32 to 7 points. It remains unclear how to taper dosage or if maintenance therapy is needed. Some authors use 150 mg/month and others 300 mg every 6 weeks, and no definite data are available.

Only a few cases of UV treated with omalizumab have been reported in the English literature.^{6–9} Our case is remarkable because of the rapid and complete response to omalizumab despite its chronic course (10 years) and resistance to immunosuppressants and antihistamines.

In conclusion, omalizumab may be a useful method to treat UV, although larger studies should be conducted to support our findings.

Learning points

- Omalizumab may be effective in UV by the same mechanism as in chronic urticaria, or it may be that there are unknown pathways to elucidate.
- Its mechanism of action may still be partially unknown, although it is known to downregulate IgE and has a good safety profile.
- Patients with refractory chronic urticaria/angio-oedema usually experience recrudescence of symptoms after stopping or even lowering omalizumab therapy, but in our case tapering was well tolerated with no relapse, and it was effective when tapered to 150 mg every 6 weeks.
- No AEs (including anaphylaxis) were noted.
- Omalizumab may be an alternative treatment for UV.

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