Methotrexate combined with omalizumab for difficult to treat urticaria

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Published in:
Clinical and Experimental Dermatology

DOI:
10.1111/ced.14359

Publication date:
2020

Document Version
Peer reviewed version

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Article type : Correspondence

Methotrexate combined with omalizumab for difficult to treat urticaria: a further step-up treatment?

Dear Editor,

Classically, chronic urticaria has been treated following a stepwise approach where Omalizumab and other immunosuppressants occupy the last step. Omalizumab and Methotrexate have both been used separately for the treatment of urticaria[1,2]. We believe combination treatment with both agents is a valuable alternative for refractory chronic urticaria and other related diseases such as urticarial vasculitis. Here we report on two patients who responded to the combination treatment.

Patient 1 is a 53-year-old woman first assessed in January 2007 with a "hive"-like eruption resolving within twenty-four hours without hyperpigmentation. She also described raised red lines after minimal stroking of her skin. Clinical findings were consistent with chronic spontaneous urticaria and symptomatic dermographism. A combination of different H1 and H2 antihistamines, Montelukast and different forms of ultraviolet phototherapy were trialled with little clinical response. In June 2010, Azathioprine was started at a dose based on TPMT enzyme activity, but it was discontinued after one-month due to drug-induced neutropenia and hepatitis. In September 2010, subcutaneous Methotrexate once weekly was introduced up to a dose of 25 mg once weekly, significantly reducing urticaria symptoms and the number of episodes. During that period, no

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other side effects were observed and blood test monitoring remained stable. Although improved, her symptoms were still intolerable and she had to reduce her work hours as activity aggravated the dermographism. In February 2015, Omalizumab was added alongside the Methotrexate and titrated up to a total of 300mg four weekly and was associated with notable clinical improvement. In March 2016, a loss of efficacy of Omalizumab was reported by the patient after 3 weeks. Thus, the dose was increased to 300mg three weekly. She is currently taking Omalizumab combined with Methotrexate, and has been so for 5 years, with good control of her urticaria and without drug related adverse effects.

Patient 2 is a 58-year-old woman with a past history of chronic spontaneous urticaria and angioedema since February 2007. She was first assessed in the Photobiology Department in April 2008 because of erythema over the dorsal arms following three to five minutes of sunlight exposure. On monochromator phototesting, an abnormal urticarial response within ultraviolet A and visible wavebands (335 to 400 nm) was found with minimal urticarial dose of 4700 $mJcm^{-2}$ at 365±30 nm [half-maximum bandwidth] waveband (reference range for delayed erythema ≥18000 $mJcm^{-2}$) nm and dose of 47000 $mJcm^{-2}$ of 400±30 nm waveband (reference ≥56000 $mJcm^{-2)}$, without abnormal delayed responses. Solar simulator showed abnormal immediate urticarial response to UVA and visible light on the dorsal hand. These results were consistent with solar urticaria. Despite investigation no underlying cause was found so this was idiopathic solar urticaria. Over years her solar urticaria fluctuated in severity both clinically and as determined on phototesting. From 2008 to 2015, she took Omalizumab 300mg every four weeks and reported clinical improvement. However, it was discontinued due to constipation. Azathioprine was trialled but not tolerated due to nausea. Following this, a four-day course of high-dose intravenous immunoglobulin was given but it was stopped due to significant leukopaenia. Later, in 2015 she started subcutaneous Methotrexate 25mg per week with good tolerance and she continued it for one year. This provided the longest period of disease control. In November 2018, she developed wheals which resolved within a few days leaving bruising of the skin in her arms after sun exposure. Lesions were reproduceable on phototesting and histopathology showed a mixed inflammatory cell infiltrate with red cell extravasation consistent with leukocytoclastic vasculitis although there was no fibrinoid necrosis. A diagnosis of urticarial vasculitis induced by sun exposure was made and she was initiated on Dapsone alongside Methotrexate. Unfortunately, she felt unwell when dapsone was increased to 50 mg once daily. As the only systemic

immunosuppressant she had tolerated was Methotrexate, in December 2019 Omalizumab was reintroduced at 150mg once a month in combination with methotrexate 25mg once weekly. After 3 months of treatment she reported a significant improvement of quality of life, with better control of the condition and without side effects. Monochromator phototesting to long UVA (365±27 nm waveband) performed on her forearm showed the same minimal urticarial dose (threshold response) as before starting the treatment, but there was a delay in the time to response compared with previous testing.

To our knowledge, this combination has not been previously reported for treatment of urticaria. We believe this is an effective treatment option when faced with refractory and severe chronic urticaria or urticarial vasculitis.

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Funding sources: None

Conflicts of interest: None to declare

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