# Treatment of Widespread Eosinophilic Cellulitis (Wells' Syndrome) with Benralizumab

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Accepted Nov 11, 2020; Epub ahead of print Nov 18, 2020

Wells' syndrome, also known as eosinophilic cellulitis, was first described in 1971. It is a rare inflammatory skin disease of unknown pathogenesis and a varying clinical presentation. Most often, the disease presents as erythematous itchy or burning plaques, but bullous, papulonodular, papulovesicular, urticaria-like and fixed drug eruption types have also been described (1). There is a wide variety of treatment options, but no standard guidelines, and treatment can be challenging. We report here a patient with widespread and recurrent eosinophilic cellulitis (EC) (Wells' syndrome) and severe eosinophilic asthma, in whom treatment with benralizumab was successful.

## CASE REPORT

A 48-year-old, otherwise healthy, woman presented to our outpatient dermatological clinic with a 2-month history of small erythematous nodules, expanding into itchy patches on the abdomen. Five months earlier, she experienced a sudden onset of severe non-allergic eosinophilic asthma, treated twice daily with 320/9 µg budesonide/formoterol, and, on 2 occasions since then, with prednisolone because of acute exacerbations. During the last prednisolone treatment, the skin lesions regressed completely, but they recurred one month later, now spreading to the extremities. On examination, several up to 10×10-cm large brown patches with prominent erythematous borders were found on the trunk and extremities (**Fig. 1**). Skin punch biopsy specimen from the border of an element demonstrated normal epidermis, with severe interstitial inflammation with eosinophilic granulocytes and flame figures throughout the papillary and reticular dermis, consistent with Wells' syndrome (**Fig. 2**).

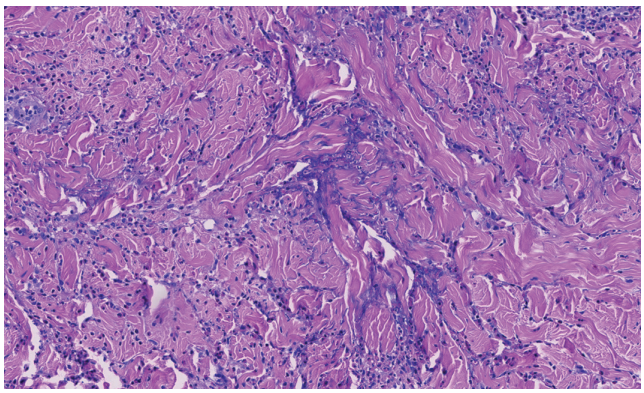

**Fig. 2. Interstitial inflammatory infiltrate with eosinophils and characteristic flame figures consisting of eosinophil granules accumulating on collagen fibres.** (Haematoxylin-eosin (H-E) stain, ×20 magnification).

During the following 6 months, the patient's skin was treated with topical clobetasol propionate 0.05%, which proved ineffective, and twice with prednisolone 25 mg (slowly discontinued over 5 weeks), clearing the lesions only temporarily. After 6 months, 50 mg dapsone was prescribed daily. At that time, the patient had widespread elements on her trunk and lower extremities, and serum eosinophilia had increased to $4.78 \times 10^9$/l. After 20 days of treatment, dapsone was discontinued due to lymphocytopaenia. At this time, the patient's asthma had worsened, despite 2 months' treatment with montelukast and an increased dose of budesonide/formoterol (640/18 µg). Therefore, it was decided to start subcutaneous injections with benralizumab, an interleukin-5 receptor α blocker, at monthly doses of 30 mg.

In the evening of the first day of benralizumab therapy, the patient felt weak with fever. The following day she recovered completely from all symptoms, and her serum

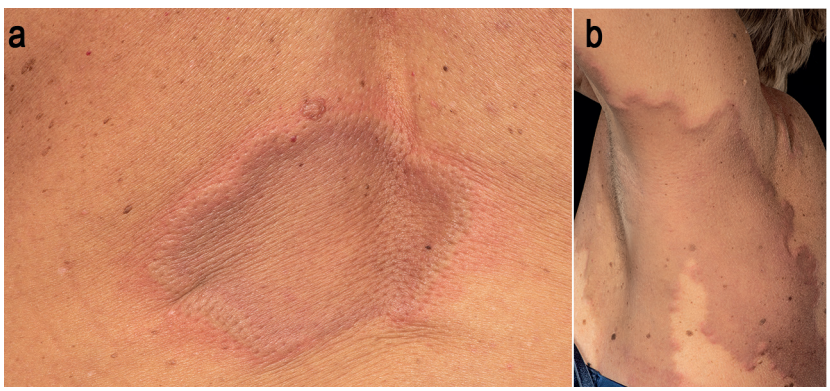


**Fig. 1. Clinical photographs during exacerbation, showing large well-demarcated brown plaques with prominent erythematous borders** on (a) the back and (b) the arm/trunk.



doi: 10.2340/00015555-3697
Acta Derm Venereol 2020; 100: adv00332

eosinophilic levels decreased to 0. During 6 months of follow-up, no breakthrough of either asthma or dermal symptoms occurred. The patient experienced no side-effects.

## DISCUSSION

To our knowledge, this is the first case of documented effect of benralizumab for the treatment of Wells' syndrome. Wells' syndrome is characterized by granulomatous eosinophilic infiltrates in the dermis. Degranulation of eosinophils is seen forming flame figures. Through the effect of the toxic granules, eosinophils have proinflammatory activity. There seems to be a close relationship between Wells' syndrome and eosinophilic granulomatosis with polyangiitis (EGPA). Case reports have demonstrated patients with Wells' syndrome developing into EGPA, suggesting that the 2 manifestations may originate from the same pathogenetic processes (2). It is, however, still discussed whether Wells' syndrome is an independent disease or could be a prodromal manifestation of EGPA (3). In the current case, the patient's symptoms (Wells' syndrome, asthma and eosinophilia) could be a manifestation of evolving EGPA, but at present, it is not possible to verify this potential relationship.

There is limited literature on the treatment of Wells' syndrome. Based on case reports and small case series, currently recommended treatments include local and oral steroids, and for therapy-resistant cases dapsone or cyclosporine (1, 4). In a few cases treatment has been successful with tumour necrosis (TNF)-α inhibitors, omalizumab (anti-IgE) and, in one patient, with mepolizumab (another interleukin-5 inhibitor) (1, 4, 5).

Benralizumab is a humanized anti-eosinophilic monoclonal antibody against the interleukin-5 receptor α subunit. It is approved for the treatment of severe uncontrolled eosinophilic asthma, and acts through direct binding to the interleukin-5 receptor α on eosinophils and by attracting natural killer cells to induce depletion of eosinophils (6). Benralizumab produces a rapid, complete and sustained depletion of eosinophils in the blood and bone marrow and an almost complete depletion in sputum and tissues (6). The eosinophilic reduction is greater than with the use of anti-interleukin-5 biologics (mepolizumab and reslizumab) (7).

Based on these results, interleukin-5 receptor α blockade with benralizumab appears to be highly effective against Wells' syndrome and should be considered in patients with widespread and refractory disease.

## ACKNOWLEDGEMENTS

The authors thank photographer Jørn A. J. Petersen for the photographic work. The patient in this manuscript has given written informed consent to publication of the case detail.

*The authors have no conflicts of interest to declare.*

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