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Benefit of benralizumab treatment in a patient with chronic symptomatic dermatographism

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Symptomatic dermatographism (SD, formerly also known as urticaria factitia) is a form of chronic inducible urticaria (CIndU) characterized by chronic itch and the development of itchy wheals upon skin exposure to friction, for example after rubbing or scratching of the skin (1). SD is one of the most common forms of CIndU and can be associated with a high burden and strong quality of life (QoL) impairment, and it often is: In a recent study, in 150 patients with SD, over half of the patients reported disturbed sleep and chronic fatigue, almost half had significantly impaired QoL, and 7%

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stated that a normal life was not possible for them, with major effects of SD on work, leisure, sports, and social activities and contacts (2). Antihistamines are the first line treatment, but many patients with SD show insufficient response, even to higher than standard doses (3). Omalizumab can be effective in the treatment of patients with SD, but is currently not licensed for this (5, 6).

Benralizumab, a humanized monoclonal anti-Interleukin-5 antibody, is effective and licensed for the treatment of severe eosinophilic asthma (4). Interleukin-5 is a major driver of eosinophilia and eosinophil recruitment to sites of inflammation. Recently, we reported that mepolizumab and reslizumab, other IL-5-targeted treatments, can result in the remission of chronic urticaria including chronic inducible urticaria (7, 8).

Here, we report the case of an 80-year old male patient with severe SD. Our patient had first developed SD 25 years ago. Over the years, he had been treated with several antihistamines including fexofenadine and cetirizine, at standard and higher doses, without significant benefit. When the patient first presented to us, his SD treatment was prednisolone, 2.5 mg daily, which it had been for months. Our attempt to reduce the dose of prednisolone resulted in a strong and immediate exacerbation of SD disease activity.

Despite his systemic glucocorticoid treatment, the patient had persistent itch, especially of the back, as well as daily wheals. His QoL was markedly impaired, and his urticaria control test (UCT) score was 6 of 16, indicative of poorly controlled SD. Trigger threshold provocation testing with the help of FricTest® showed severe SD with the induction of itchy wheals by 4 of 4 pins (Figure 1). In addition to his SD, our patient had severe allergic eosinophilic asthma, which was uncontrolled despite oral and topical steroids, LABA, LAMA, as well as other treatments including theophylline.

Because of his asthma, we initiated treatment with benralizumab (30 mg, every 4 weeks, subcutaneously), which was first given in January, a second time in February, and again in March of 2019. When our patient reported back to us 4 weeks after the first injection of benralizumab, his SD had improved markedly. He was now able to tolerate exposure to friction much better, and his chronic itch had significantly improved. At the time, our patient reported that the last few days had been slightly worse as compared to the first three weeks after the first treatment. After the second treatment with benralizumab, the SD improved further for three weeks, showing moderate worsening during week four. Further improvement for three weeks was noted after the third injection of benralizumab. At the end of the first three months of treatment, provocation testing with FricTest® was negative (0 of 4 pins produced a wheal; Figure 1), the pruritus has subsided completely, the patient's quality of life had improved significantly, and his UCT score was 13 of 16,

indicative of controlled disease. Our patient also improved markedly with respect to his asthma with major improvement after the first injection and complete response following the second injection of benralizumab. Exhaled FeNO (39 ppb), blood IgE (270 KU/L) and eosinophil levels (1040 Eos/ul) were elevated before treatment. Following the 1st injection of benralizumab, FeNO levels decreased to 22 ppb and blood eosinophil levels dropped to 24 cells/ul measured 4 weeks after the first treatment. FEV1 increased after the 1st injection from 1.9 L/min (68% pred.) at baseline to 2.3 L/min (80% pred.).

To our knowledge, this is the first report of benralizumab treatment in a patient with SD or other forms of chronic urticaria. Before this treatment, our patient had long-standing, severe, and treatment-resistant SD. Treatment with benralizumab, for three months, effectively reduced SD disease activity and improved QoL. Our patient is now free of itch and able to expose himself to virtually all triggers that had previously resulted in the development of itchy wheals.

We cannot explain, at this point, how the treatment with benralizumab helped our patient. Chronic urticaria including SD is a mast cell-driven disease and held to involve the degranulation of skin mast cells and the release of proinflammatory mediators including histamine. What causes mast cell degranulation in patients with CIndU including SD is unknown. The wheals of SD, unlike those of chronic spontaneous urticaria, are not typically characterized by infiltrating eosinophils or other inflammatory cells. SD and other forms of CU do not typically come with eosinophilia. Our patient had high eosinophil blood numbers, most likely linked to his asthma, before treatment, and his eosinophil counts were reduced to normal after three months of treatment. One may speculate that the effects of benralizumab on SD, in our patient, are linked to the numbers of eosinophils in his blood. This is supported by the observation that short periods of exacerbation of SD occurred before the second and the third application of benralizumab, and these was paralleled by increased blood eosinophil numbers. Future studies will have to show if benralizumab can be of benefit in patients with SD who do not have concomitant eosinophilic asthma and eosinophilia. Further studies should also characterize the role of eosinophils in SD and other forms of CU as well as the mechanisms of action of benralizumab in SD. Also, it would be interesting to investigate whether other IL-5-targeting treatments can be of benefit in the treatment of patients with antihistamine-resistant SD and other forms of CIndU.

In conclusion, the benefit of treatment with benralizumab, experienced by our patient with SD suggests a role for interleukin-5 and eosinophils in the pathogenesis of this condition. Benralizumab and other interleukin-5-targeted treatments may be considered as treatment options in otherwise treatment-resistant patients with SD.

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Figure legends

Figure 1. Results of skin provocation testing including trigger threshold measurements before and 3 months after the start of treatment with benralizumab

Left: Positive responses, i.e. itchy wheals, to scratching with all four pins of FricTest[®], before benralizumab treatment. Negative responses, i.e. erythema without whealing or itch, to all four pins of FricTest[®], three months after the initiation of benralizumab treatment.

Figure 1

