



Letters

Dupilumab as a novel therapy to treat adrenergic urticaria

Adrenergic urticaria (AU) is a rare and infrequently reported disease that presents with intermittent outbreaks of stress-induced diffuse pruritic urticarial papules. First described in 1985,¹ there has been growing literature further elucidating the mechanism of the disease and novel therapeutic options. A frequently occurring challenge in the diagnosis of AU is differentiating it from the more common cholinergic urticaria (CU). In AU, the papules are surrounded by halos of hypopigmented and vasoconstricted skin, whereas in CU, the small papules are surrounded by large red flares.² Furthermore, the triggers for AU include trauma, emotional upset, coffee, chocolate, and ginger, whereas the triggers for CU are stress, exercise, and diaphoresis.³

A proposed mechanism of AU is a sympathetic hyperactivity response resulting in both epinephrine and norepinephrine release. The epinephrine causes vasoconstriction, appearing as the halo portion of the AU lesion, whereas the norepinephrine release causes cutaneous mast cell degranulation resulting in erythema, vasodilation, and edema, appearing as the erythematous center of the AU lesion.³ Interestingly, AU is associated with postural orthostatic tachycardia syndrome (POTS), in which there is also hyperactivity of the sympathetic nervous system.⁴

The diagnosis of AU can be made by administering an intradermal injection of adrenaline or noradrenaline,⁵ which induces the rash, or clinically by observing the response to propranolol, which suppresses the rash and reduces further exacerbations. Although the rash of AU is usually improved with trigger avoidance, propranolol, and antihistamines, there are few other documented treatments. Such treatments, as documented in case reports, include oral clonazepam and omalizumab injections, which showed improvement of symptoms.^{6,7} Here, we present the first known case of AU responding to dupilumab injection therapy.

An 18-year-old man with POTS developed the characteristic rash of AU (Fig 1), which was triggered by heat, stress, and exercise. Laboratory results revealed elevated serum immunoglobulin E (134 IU/mL); both tryptase and urine 5-hydroxyindoleacetic acid were within the reference range. The skin biopsy of the papules was nondiagnostic and showed lymphohistiocytic infiltrate associated with eccrine ducts in the dermis. The patient was initially treated for presumed CU, yet he was nonresponsive to high-dose second-generation H₁-antihistamines, H₂-antihistamines, montelukast, dapson, and omalizumab monthly injections. The diagnosis was reconsidered given his poor response to treatment, and he was subsequently diagnosed as having AU given the appearance of his rash and a diagnosis of POTS. A potential weakness of this case report is that the patient did not receive an intradermal injection of adrenaline or noradrenaline for definitive diagnosis. In addition, the patient does not fit the typical picture of AU because his triggers

were more consistent with CU. However, his association with POTS and the appearance of the rash make AU a more likely diagnosis. After failing several treatments and given the severity of his symptoms, the patient was started on dupilumab monthly injections, and within 2 weeks, his rash resolved completely. The patient originally had good control of his symptoms with monthly dupilumab, propranolol 20-mg twice daily, and an antihistamine. However, in the summer of 2019, the patient had a flare-up of symptoms owing to hot weather and resumption of classes, so his propranolol was uptitrated to a maximum dose of 60-mg twice daily and his symptoms resolved completely. During this period, his POTS symptoms were not exacerbated. Unfortunately, in the spring of 2020, his dupilumab injections were temporarily paused owing to the coronavirus disease 2019 pandemic, and his symptoms recurred. The patient is soon to be restarted on therapy; once his symptoms



Figure 1. Diffuse pruritic urticarial papules surrounded by halos of hypopigmented and vasoconstricted skin seen on the torso.

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resolve, the ultimate goal would be to space the dupilumab injections with the hopes of weaning it off.

The treatment options for AU are limited and not all patients will respond to the previously documented regimens, including propranolol and antihistamines. As illustrated by this case, dupilumab injections may be an adjuvant therapeutic option in AU. Dupilumab is a receptor antagonist that binds to the alpha subunit of the interleukin (IL)-4 receptor and modulates signaling of both the IL-4 and IL-13 pathways.⁸ Therefore, a possible mechanism for dupilumab decreasing the severity of the rash in AU is by preventing the progression of the IL-4 pathway, thus preventing the increased expression of FcεR1 on B cells, mast cells, and basophils. By decreasing the production of FcεR1, there is an overall reduction in their cross-linkages with immunoglobulin E on the mast cell's surface, which decreases mast cell activation and histamine release. Although propranolol partially controlled his symptoms, dupilumab was necessary for complete resolution.

Brian Goodman, MD*
Sunit Jariwala, MD†

*Department of Medicine, Montefiore Medical Center
Bronx, New York

†Department of Allergy & Immunology, Montefiore Medical Center,
Bronx, New York
brgoodma@montefiore.org

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