A successful case of dupilumab treatment for severe uremic pruritus

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Uremic pruritus (UP) is highly burdensome and difficult to treat. Previous studies implicated interleukin (IL)-31 in the pathogenesis of UP.[1,2] IL-31 expression is upregulated by T-helper 2 cells in several pruritic disorders, including atopic dermatitis and cutaneous T-cell lymphoma.[2] Yet, the role of T-helper 2 or other cytokines in UP has not been fully elucidated. We present a case of UP successfully treated with dupilumab, a fully human monoclonal antibody that targets IL-4 receptor α and blocks signaling of IL-4 and IL-13.

Abbreviations used:

IL:	interleukin
NBUVB:	narrow-band ultraviolet B phototherapy
UP:	uremic pruritus

CASE

A 45-year-old woman was seen at the dermatology practice at Northwestern Medicine for management of severe generalized pruritus. After extensive workup, polycystic kidney disease was diagnosed. The pruritus was initially well controlled with narrow-band ultraviolet B phototherapy (NBUVB) 1 to 2 times per week (>100 sessions). However, she experienced progressive worsening of renal function and underwent renal transplant at age 53. The pruritus resolved immediately after transplantation, and phototherapy was discontinued.

At age 55, the generalized pruritus recurred, and renal function slowly began to worsen. The pruritus did not resolve after treatment with NBUVB 2 to 3 times per week (97 sessions) combined with at least 1 of the following: doxepin, 20 mg daily, aprepitant, 40 mg twice daily, pregabalin, 100 mg daily, naltrexone, 100 mg daily, mirtazapine, 15 mg daily, topical mometasone, pramoxine and menthol, numerous emollients, and other over-the-counter and homeopathic therapies.

Her medical history was significant for stable hypertension, and history of hay fever diagnosed at age 12 years, which resolved in adulthood. She denied any personal or family history of eczema or asthma. Physical examination was notable for numerous excoriations on the neck, chest, abdomen, back, arms, hands, legs and feet. No primary inflammatory lesions were observed at any encounter.

Pertinent negative laboratory tests included thyroid-stimulating hormone, bullous pemphigoid antigen 1/2, peripheral hemoglobin, hematocrit, eosinophils, liver enzymes, calcium, phosphorus, hepatitis B and C, HIV, celiac panel (serum transglutaminase, gliadin [Deamidated] immunoglobulin A autoantibody, total immunoglobulin A), and serum immunoglobulin E.

At age 61, subcutaneous dupilumab was started with a 600-mg loading dose followed by 300 mg every other week. NBUVB and gabapentin were initially continued. At baseline, she reported severe and almost daily itch, moderate skin pain, frequent sleep disturbance, and moderate quality-of-life

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Table I. Improvement of itch intensity, sleep disturbance, and quality of life and decreased concomitant treatments after starting dupilumab

Variable	Baseline	Months of treatment with dupilumab					
		1	2	3	4	5	6
Peak pruritus NRS in the past 7 days	8/10	8/10	8/10	2/10	2/10	3/10	1/10
Average pruritus NRS in the past 7 days	7/10	7/10	6/10	2/10	2/10	3/10	1/10
Numbers of days with itch in past 7 days	7	7	6	4	2	3	1
Number of nights itch awoke from sleep in past 7 days	2	1	6	0	0	0	0
Average pain NRS in the past 7 days	5/10	2/10	0/10	0/10	0/10	0/10	0/10
Number of days with dry skin in the past week	7	6	5	5	3	5	3
Number of days with bleeding skin in the past week	2	1	0	0	0	0	0
Dermatology Life Quality Index	12/30	4/30	3/30	1/30	2/30	1/30	1/30
Mean ItchyQOL score	3.8/5	1.8/5	1.4/5	1.7/5	1.3/5	1.1/5	1.1/5
Concomitant treatments	NBUVB twice weekly Gabapentin 600 mg/d	NBUVB twice weekly Gabapentin 600 mg/d	NBUVB twice weekly Gabapentin 600 mg/d	NBUVB twice weekly Gabapentin 500 mg/d	NBUVB every 10 days	NBUVB every 10 days	NBUVB every 10 days

NRS, Numeric rating scale.

disturbance (Table I). All scores improved to clear or almost clear by 6 months, and she was able to taper or discontinue almost all concomitant treatments. She did not experience any adverse events from dupilumab. Her renal function remains stable.

DISCUSSION

UP was found to affect 84% of patients and is the second most common symptom in end-stage renal disease patients in a study of 49 treated without dialysis.[3] Most patients with UP reported that it was at least somewhat distressing (82%), and 43% reported that it was very distressing.[3] Moderate-to-severe UP was also found to affect 41.7% of patients with end-stage renal disease on dialysis in a large-scale multinational observational study.[4]

There is a need for safe and effective treatments for UP. Many off-label treatments have been used for UP, including phototherapy, neuroleptics, and antidepressants, each with variable short-term efficacy, limited long-term efficacy, and potential for numerous serious adverse events.[5] This case suggests that dupilumab may be both a safe and effective therapy in some cases of severe UP.

The mechanism by which dupilumab may work in UP is unknown. A recent study found that type 2 cytokines directly activate sensory neurons in both mice and humans.[6] Further, chronic itch was found to be mediated by signaling via interleukin-4 receptor α expressed on the surface of sensory neurons and intracellularly through Janus kinase 1.[6] It may be that UP patients have increased expression of IL-4 and/or IL-13. If so, then dupilumab may directly inhibit itch by blocking the signaling of IL-4 and/or IL-13 on sensory neurons. Previous findings suggest that IL-31 plays an important role in the pathogenesis of UP.[1,2] It is possible that dupilumab indirectly inhibits itch by decreasing production of IL-31 by T helper 2 cells. Future studies are needed to determine the mechanism of action for improved itch with dupilumab treatment.

CONCLUSIONS

Dupilumab resulted in significant improvement of severe UP in the setting of stage 3 chronic kidney disease. Future studies are needed to confirm this case and determine the overall efficacy of dupilumab in UP.

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