

LETTER TO THE EDITOR

An urticarial drug eruption caused by tofacitinib for alopecia universalis

New molecularly targeted therapeutics, including tofacitinib, are proving beneficial in patients with treatment-refractory alopecia areata (AA) and alopecia universalis (AU). The janus kinase and signal transducer and activator of transcription (JAK-STAT) pathway is an intracellular signaling pathway, upon which many different proinflammatory signaling pathways converge. In AA, JAK-STAT-dependent cytokines including interferon gamma and interleukin-15 (IL-15) drive activation of autoreactive T-cells which target the hair follicles (Damsky & King, 2017). Oral JAK 1/3-inhibitors such as tofacitinib, have recently shown success in hair regrowth, with 77% of patients with AA experiencing hair regrowth and 58% achieving >50% improvement in their Severity of Alopecia Tool Score (Triyangkulsri & Suchonwanit, 2018). Reported side-effects included Grade I and II infections, elevated liver transaminase, and cholesterol (Triyangkulsri & Suchonwanit, 2018). Long-term safety reports of tofacitinib for treatment of rheumatoid arthritis suggest an increased risk of herpes zoster, opportunistic infections, tuberculosis, and skin malignancies (Cohen et al., 2017). We report a case of drug-induced urticaria due to tofacitinib during treatment of AU.

A 21-year-old man presented with a history of longstanding AU (>10 years). Previous treatments included topical diphenylcyclopropenone, topical and intralesional corticosteroids, with nil improvement. The impact of AU on his life was significant, with a Dermatology Life Quality Index score of 18/30. He wore false eyebrows and caps at all times, to reduce anxiety in social and work settings. He had no significant past medical history, regular medications, allergies or atopic history. Oral Tofacitinib 5 mg twice daily was commenced. After 8 weeks, signs of regrowth were noted on his scalp, eyebrows, and jawline.

After 14 weeks of treatment he complained of intensely pruritic, erythematous, migratory wheals on both forearms (Figure 1a), which moved to his legs. The reaction was non-painful and did not involve mucosal surfaces. He denied symptoms of dyspnoea, wheeze, and angio-oedema. He had no symptoms of intercurrent illness, and denied taking any other medications—over-the-counter or prescribed. Full blood examination revealed normal eosinophil ($0.3 \times 10^9/L$) and immunoglobulin E (21 kU/L) counts. He was prescribed oral cetirizine 10 mg twice daily and topical betamethasone dipropionate (0.05%) cream daily. After 4 days of treatment, the reaction began to settle (Figure 1b). Given the impressive hair regrowth, the patient opted to remain on tofacitinib.

In a study examining the effect of tofacitinib in patients with hypereosinophilic syndrome, a significant reduction in blood eosinophils

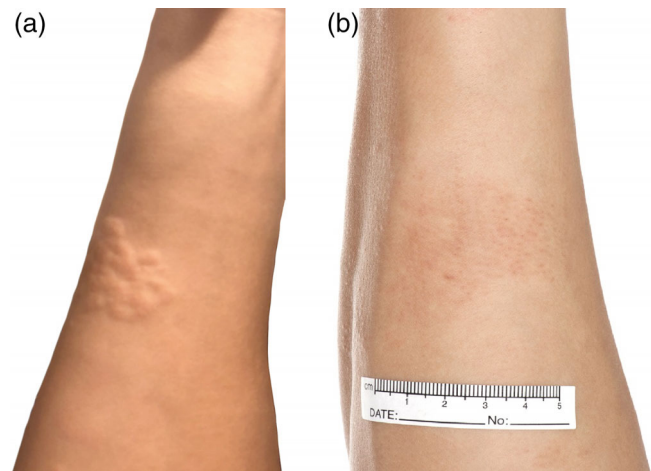


FIGURE 1 (a) A young male with erythematous, oedematous wheals emerging on the right forearm. (b) Resolving erythematous reaction of the right forearm after 4 days of corticosteroid treatment

was noted (King, Lee, & Choi, 2017). This was hypothesized due to JAK1 inhibition, which inhibits the activation of STAT3 target genes, which are critical for T-helper 2 cell differentiation and the production of eosinophil-promoting cytokines such as IL-4, IL-5, and IL-13 (King et al., 2017). Conversely, it was noted by Kirshenbaum et al., that tofacitinib had no dose-response reduction in human mast cell degranulation or prostaglandin D2 production (Kirshenbaum, Bai, & Metcalfe, 2018). The mechanism by which tofacitinib causes urticaria warrants further investigation, particularly its effects on downstream cytokine adhesion and proliferation.

Given the impressive hair regrowth, lack of mucosal or systemic side-effects and control with antihistamines, tofacitinib did not warrant cessation. Tofacitinib is currently in Phase III studies, which are likely to provide greater insight into the frequency of urticarial drug eruptions. Clinicians should be aware of urticaria as a possible adverse event of tofacitinib treatment.

CONFLICT OF INTERESTS

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