Title: Folliculitis decalvans responsive to tofacitinib: a case series

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Folliculitis decalvans (FD) is a predominately neutrophilic, cicatricial alopecia that preferentially affects the vertex of the scalp with pustules, crusting and tufted hairs.\textsuperscript{1} Mild disease responds to antiseptic shampoos and topical clindamycin, however severe disease may be chronic, progressive and refractory to treatment.\textsuperscript{2} Conventional treatments for severe disease include antibiotics, corticosteroids and isotretinoin. Successful treatment of folliculitis decalvans with adalimumab, infliximab, secukinumab, Nd-YAG laser and photodynamic therapy (PDT) have previously been described in case reports.\textsuperscript{3,4}

We report 3 patients with refractory FD responding to the oral Janus Kinase (JAK) inhibitor tofacitinib. Prior to commencing treatment all patients had pre-screening laboratory investigations (including complete blood count, metabolic panel, fasting lipid panel), infection screen (QuantiFERON-TB Gold, screening for HIV, hepatitis B and C) and were counselled on the possible adverse effects of tofacitinib (including infection risk, headaches, gastrointestinal upset, acne, transaminitis and dyslipidaemia). In the absence of a validated outcome measure for FD, we considered the following parameters when assessing response to treatment: photographic improvement; subjective improvement in symptoms; maintenance of the same therapeutic dose; and ability to taper therapy.

**Case 1:** A 42-year-old Caucasian male had a longstanding history of FD affecting the vertex. Previous unsuccessful treatments included: hydroxychloroquine, isotretinoin, ciclosporin, minocycline, rifampicin, intralesional steroids and topical therapy (clindamycin, mupirocin) (see Table 1). Tofacitinib, 2.5mg twice daily, was commenced in combination with oral clarithromycin, oral minoxidil and topical treatment (clindamycin and steroids) (Table 1). Ciclosporin 100mg BD (2.5mg/kg) was maintained to prevent disease flare. Subjective and objective improvement, evidenced by resolution of pustules and reduced bleeding, was noted following 4 months of treatment. Ciclosporin was subsequently tapered and
discontinued, while tofacitinib was reduced to 4mg daily. Clinical and photographic improvement was observed (Figure 1(a)) with a self-reported 80% improvement in itch and 100% resolution of pain at 9 months. The response was sustained until tofacitinib was interrupted, due to an upper respiratory tract infection, resulting in a subsequent flare of FD just 1 month later.

**Case 2:** A 36-year-old Ethiopian male with recalcitrant FD had failed treatment with prednisolone, dapsone, ciclosporin, mycophenolate mofetil, isotretinoin, topical clobetasol, intralesional steroids, oral/topical antibiotics and minoxidil. Tofacitinib 2.5mg daily was added to current treatment of minoxidil, rifampicin 300mg BD, clarithromycin 300mg BD and clindamycin shampoo. Tofacitinib was well tolerated, apart from a transiently elevated total cholesterol and mild eosinophilia, and resulted in a rapid resolution of active inflammation within 3 months of commencing therapy (Figure 1(b)). After 16 months on a stable dose of tofacitinib and disease inactivity, the patient discontinued the medication due to travel, but relapsed 6 months later.

**Case 3:** A 31-year-old female with an 8-year history of FD commenced tofacitinib 2.5mg daily, while continuing minoxidil, spironolactone, clarithromycin, clindamycin shampoo and topical steroids, having failed to respond to ciclosporin, intralesional triamcinolone. Hair shedding reduced and pustules resolved within a month of starting tofacitinib (Figure 1(c)), while symptomatic (reduced itch and pain) and clinical improvement was recorded at 5 month review, without any adverse effects. Disease remission was maintained for 22 months before relapse, despite cessation of tofacitinib by the patient after 10 months.

This small case series demonstrates the efficacy of tofacitinib in the treatment of recalcitrant FD. Tofacitinib is a selective JAK 1/3 inhibitor that has been used to treat a
number of inflammatory diseases including rheumatoid and psoriatic arthritis, psoriasis, atopic dermatitis, systemic lupus, vitiligo as well as alopecia areata (AA) and lichen planopilaris (LPP). Tofacitinib inhibits signalling of Interferon (IFN)-γ, Interleukin (IL)-2, IL-4, IL-6, IL-7, IL-9, IL-15 and IL-21 that are thought to play a key roles in cutaneous inflammation. Moreover, inhibition of the JAK-STAT pathway has previously been shown to promote hair growth by stimulating the proliferation and/or activation of hair follicle stem cells. The immunopathogenesis of FD remains unclear, however, microbial dysbiosis is believed to be a key feature. *S. aureus* leads to production of numerous cytokines, thereby attracting neutrophils that cause hair follicle destruction. Resident skin T-lymphocytes may also be activated by microbial antigens and/or superantigens prompting release of several proinflammatory (e.g. IFN-γ) and profibrotic factors (e.g. IL-4).

Limitations of this series include the small sample size and use of concurrent medication. Though latent benefit and potential synergism are possible, it is worth noting the recalcitrant nature of FD in each patient before tofacitinib was introduced. Relapse after treatment cessation occurred at variable time points in all 3 patients; a recognised feature of FD, even in mild cases. While durable remission remains the goal, tofacitinib and JAK inhibition represents a possible treatment avenue. Larger, long-term follow-up studies to assess its real-world effectiveness in this condition are needed to validate this.
References


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<table>
<thead>
<tr>
<th>Patient No./Sex/Age, y</th>
<th>Disease duration prior to treatment, y</th>
<th>Treatments before Tofacitinib</th>
<th>Daily Tofacitinib dosage</th>
<th>Total treatment duration (months)</th>
<th>Concurrent therapies*</th>
<th>Side effects of treatment**</th>
</tr>
</thead>
<tbody>
<tr>
<td>1/M/42</td>
<td>12</td>
<td>Hydroxychloroquine, isotretinoin, ciclosporin, minocycline, rifampicin, minoxidil. Topical agents: mupirocin, clindamycin, clobetasol propionate 0.05%. Intralesional triamcinolone</td>
<td>2.5mg twice daily (8 months) 4mg once daily (8 months)</td>
<td>16</td>
<td>Minoxidil, ciclosporin (for 8 months), clarithromycin, clindamycin shampoo, clobetasol propionate 0.05%</td>
<td>LFT derangement (GGT 5.6xULN, ALT 2.2xULN, AST 1.4xULN), indigestion</td>
</tr>
<tr>
<td>2/M/36</td>
<td>&gt;5</td>
<td>Prednisolone, dapsone, ciclosporin, mycophenolate mofetil, isotretinoin, cephalaxin, minoxidil. Topical agents: clobetasol propionate 0.05%, clindamycin</td>
<td>2.5mg once daily</td>
<td>16</td>
<td>Rifampicin (for 2 months), minoxidil, clarithromycin, clindamycin shampoo (for 1 month)</td>
<td>Eosinophilia (1.5xULN), elevated total cholesterol (1.35xBLV), mild fatigue</td>
</tr>
<tr>
<td>3/F/31</td>
<td>8</td>
<td>Ciclosporin, minocycline, minoxidil, spironolactone Topical agents: clindamycin, clobetasol propionate 0.05%. Intralesional triamcinolone</td>
<td>2.5mg once daily</td>
<td>10</td>
<td>Minoxidil, spironolactone, clarithromycin, clindamycin shampoo, clobetasol propionate 0.05%</td>
<td>None</td>
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</tbody>
</table>

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Abbreviations: ALT, alanine aminotransferase; AST, aspartate aminotransferase; BD, twice daily; BLV, baseline value; GGT, gamma-glutamyl transferase; LFT, Liver function tests; OD, once daily; ULN, Upper limit of normal.

* Concurrent therapies were continued throughout whole tofacitinib treatment duration unless otherwise specified and do not represent novel treatments but rather a continuation from pre-tofacitinib.

** All side effects were transient unless otherwise specified. Maximum level of derangement reported.
FIGURE legends:
Figure 1: Clinical response to tofacitinib in 3 patients with refractory Folliculitis decalvans

(a) Patient 1: pre-treatment and after 17 months of treatment
(b) Patient 2: pre-treatment and after 12 months of treatment
(c) Patient 3: pre-treatment and after 3 months of treatment