



Treatment of Crohn's Disease and Concomitant Alopecia Areata With Tofacitinib

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ABSTRACT

Alopecia areata (AA) is a type of immune-mediated hair loss and is reported in patients with inflammatory bowel disease. This suggests that there might be a shared molecular pathway in the pathogenesis of AA and inflammatory bowel disease. In addition, tumor necrosis factor-alpha antagonists are also rarely associated with new-onset AA. We present a patient with Crohn's disease treated with adalimumab who developed AA that rapidly progressed to alopecia totalis and universalis. We describe the use of tofacitinib, a Janus kinase 1/3 inhibitor, to not only successfully treat the AA but also maintain her Crohn's disease.

INTRODUCTION

Crohn's disease (CD) is a chronic inflammatory condition of the gut which is attributed to the dysregulation of helper T cells, such as T helper 1 (T_H1) cells and interleukin 17-producing T helper (T_H17) cells.¹ Alopecia areata (AA) is an immune-mediated, non-scarring form of hair loss that is mainly mediated by CD8⁺ cytotoxic T cells.² Previous studies have shown that AA may develop in patients with immune-mediated diseases, including inflammatory bowel disease (IBD).^{3,4} Interferon- γ (IFN- γ) might be a common molecule contributing to the pathogenesis of both CD and AA because IFN- γ is produced by T_H1 cells and by CD8⁺ T cells.⁵ IFN- γ signaling depends on Janus kinases (JAKs), particularly JAK1 and JAK2, suggesting that JAK inhibitors may be able to control these conditions.⁵ Tumor necrosis factor-alpha (TNF- α) antagonists are often prescribed in patients with IBD. However, TNF- α antagonists sometimes induce new-onset AA.⁶⁻⁹ We present a patient with CD treated with adalimumab who developed AA that progressed to alopecia totalis and universalis. Tofacitinib successfully treated her hair loss and maintained her CD.

CASE REPORT

A 37-year-old woman was diagnosed with ileocolonic CD at the age of 35 years. Colonoscopy showed congested, erythematous, friable mucosa in the rectosigmoid colon and deep ulcerations in the terminal ileum. Pathological findings revealed chronic active enteritis and colitis. She achieved clinical remission with adalimumab 40 mg subcutaneous injection, which required dose escalation to 40 mg subcutaneous weekly. C-reactive protein and fecal calprotectin were high (11.2 mg/L and 312 μ g/g, respectively) on starting adalimumab but then normalized to <3 mg/L and <15.6 μ g/g, respectively.

After 2 years of adalimumab therapy, she developed AA (Figure 1). Over 2 months, it rapidly progressed to alopecia totalis despite treatment with topical steroids and minoxidil (Figure 1). At the time of her evaluation, physical examination showed a few hundred hairs scattered diffusely over the scalp and mild nonfocal thinning in the eyebrows and lashes. Patchy hair loss was also observed on her extremities and body. Therefore, she was switched from adalimumab to tofacitinib 10 mg daily (5 mg BID). Tofacitinib did not initially alleviate her hair loss. She developed some CD-related symptoms, including diarrhea and abdominal pain, but fecal calprotectin was <15.6 μ g/g. The dose of tofacitinib was increased to 15 mg daily (10 mg qAM and 5 mg qPM) in conjunction with her dermatologist at 6 months after the initiation of tofacitinib to control AA. Two months later, her hair began to grow and continued to grow as time progressed (Figure 1). Finally, she achieved complete regrowth of her hair at 5 months after tofacitinib dose escalation (Figure 1). Her CD-related symptoms improved with oral budesonide 9 mg daily. After 8 weeks, the budesonide was discontinued, and she remained on tofacitinib 15 mg daily.



Figure 1. Clinical course of alopecia (A) patchy hair loss while on adalimumab, (B) progressed to alopecia totalis, (C) clinical image of alopecia 2 months after the dose escalation of tofacitinib, (D) 3 months after the dose escalation of tofacitinib, and (E) 5 months after the dose escalation of tofacitinib.

DISCUSSION

Our study demonstrates that tofacitinib successfully treated AA in a patient with CD who had been receiving adalimumab. AA has a well-described association with immune-mediated diseases. A Taiwanese nationwide study including 4,334 patients with AA reports a significant association between AA and other autoimmune diseases.³ Previous studies reported that the prevalence of AA in patients with IBD is higher than in the general population, suggesting that both of these diseases may have a common molecular pathway.^{1,2,4,10,11}

Meanwhile, several reports suggest that TNF- α antagonists might be a trigger for alopecia.^{6–9} A retrospective cohort study including 917 consecutive patients with IBD who initiated TNF- α antagonists showed that 264 patients (29%) developed skin lesions and only 5 patients (4 CD and 1 ulcerative colitis) developed new-onset alopecia after a median 2.2 years of TNF- α therapy.¹² Pathological characteristics of TNF- α antagonist-induced alopecia were reported as psoriasiform changes or folliculitis decalvans.^{6–9} If its pathogenesis is similar to psoriasis, the development of alopecia might be associated with IFN- γ -producing dermal plasmacytoid dendritic cells.¹³ Given that TNF- α can suppress the production of IFN- γ in the dermal plasmacytoid dendritic cells, TNF- α antagonism might increase the local expression of IFN- γ and activate IFN- γ signaling that depends on the JAK1 activity. This mechanism may contribute to the migration of T_H17 or T_H1 cells into the scalp and the subsequent development of psoriatic alopecia.^{4,13,14} In this case, the patient had been using adalimumab before the development of AA, suggesting that adalimumab might be one of the possible causes for her alopecia. Although TNF- α antagonist-induced alopecia might have a different mechanism from AA in which IFN- γ -producing CD8⁺ T cells is a key mediator, IFN signaling which depends on the activity of JAKs, particularly JAK1, would be a common target to treat either condition.² Given that her alopecia improved after tofacitinib dose escalation, this improvement may be attributed to tofacitinib use rather than adalimumab discontinuation.

Tofacitinib, an oral JAK1/3 inhibitor, has been approved for patients with rheumatoid arthritis or psoriatic arthritis who failed methotrexate and patients with ulcerative colitis who

failed anti-TNF- α therapy.¹⁵ Regarding tofacitinib use for AA, a recent meta-analysis showed that the pooled good/complete hair regrowth rate was 54.0% (95% confidence interval, 46.3%–61.5%), although large-scale randomized controlled trials have not yet been conducted.¹⁶

As for CD, tofacitinib did not show a significant improvement in clinical remission at week 8 of induction and at week 26 of maintenance in a phase 2b clinical trial.¹⁷ An open-label 48-week extension phase 2 trial showed that approximately 30% of patients with CD who were not in remission at baseline discontinued tofacitinib because of insufficient clinical response.¹⁸ In our patient, her CD-related symptoms initially worsened while off adalimumab and on tofacitinib. The rapid response to ileal release budesonide suggests that she likely did suffer from mild CD relapse. The alternative hypothesis was the nocebo response when she stopped her adalimumab. Her stable clinical picture of normal laboratory results subsequently suggests this may be the case. Although the phase 2 trial of tofacitinib did not show significant benefit in CD, it is important to recognize that some patients did respond to it. A recent multicenter real-world experience with tofacitinib in CD suggests that it is effective in some patients.¹⁹ If needed, a more selective JAK inhibitor may be reasonable next. Early phase randomized controlled trials demonstrate that upadacitinib and filgotinib, both JAK 1 inhibitors, are effective in a significant proportion of patients with CD.²⁰

DISCLOSURES

Author contributions: S. Akiyama wrote and approved the manuscript. A. Lin and C. Traboulsi reviewed the literature and revised the manuscript for intellectual content. DT Rubin edited the manuscript, revised it for intellectual content, and is the article guarantor.

Financial disclosures: DT Rubin has received grant support from Abbvie, Genentech/Roche, Janssen Pharmaceuticals, Prometheus Laboratories, Shire, and Takeda, and has served as a consultant for Abbvie, AbGenomics, Allergan Inc., Biomica, Boehringer Ingelheim Ltd., Bristol-Myers Squibb, Celgene Corp/Syneos, Check-cap, Dizal Pharmaceuticals, GalenPharma/Atlantica,

Genentech/Roche, Gilead Sciences, GlaxoSmithKline Services, Ich-nos Sciences S.A., InDex Pharmaceuticals, Janssen Pharmaceuticals, Lilly, Narrow River Management, Pfizer, Prometheus Laboratories, Reistone, Shire, Takeda, and TechLab Inc. S. Akiyama, A. Lin, and C. Traboulsi: None.

Informed consent was obtained for this case report.

Received December 21, 2020; Accepted May 7, 2021

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