SHORT COMMUNICATION

Tofacitinib for Treatment of Alopecia Areata: Real-world Evidence and Factors Associated with Therapeutic Response

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Alopecia areata (AA) is a common non-scarring type of alopecia. The severity of AA varies from mild to severe cases of generalized alopecia of scalp and body (1). A wide variety of treatments have been used in management of AA (2). Severe and extensive cases of AA, are commonly treated with systemic drugs, including corticosteroids (3) or immunosuppressive agents (4). However, lack of response and side-effects are often associated with these treatments. Janus kinase inhibitors (JAKi) have emerged as an alternative for treatment of severe cases of AA, which act via intracellular interruption of the JAK-STAT pathway (5). Tofacitinib is a potent, selective JAKi that preferentially inhibits JAK1 and JAK3 (6). Although this drug has been used previously as an off-label treatment for AA (7, 8), real-world data are scarce (9). Therefore, the aim of this study is to assess the effectiveness and safety of oral tofacitinib treatment in a prospective cohort of patients with severe AA in a real-world setting.

MATERIALS AND METHODS

An observational study was performed to assess the effectiveness and safety of tofacitinib treatment in patients with severe alopecia. All the patients who attended the Trichology Unit (Hospital Universitario Virgen de las Nieves, Granada, Spain) who were candidates to start tofacitinib treatment were invited to enrol in the study. All patients were informed about the off-label use of the drug, and gave their written informed consent for both the treatment and inclusion in the study.

Patients with a clinical diagnosis of AA who were candidates for tofacitinib treatment, and who failed to respond to previous topical therapy and oral corticosteroid treatment for a minimum period of 3 months were included. Basal Severity of Alopecia Tool II (SALT II) score was > 50%; or > 20% if the patient self-reported impairment in quality of life.

The patients were assessed on the day of initiation of tofacitinib treatment and subsequently every 3 months until the treatment was discontinued or changed. The main variables included: (*i*) SALT II score (10); (*ii*) the presence of alopecia of the eyebrows; (*iii*) clinical data (age of onset, disease duration); and (*iv*) treatment data (dosage schedule, safety variables). Statistical analyses were performed using JMP version 9.0.1 (SAS Institute, North Carolina, USA).

RESULTS

All of the 17 patients who were invited to participate in the study were included. Mean ± standard deviation (SD) age was 33 ± 19 years, with a majority of female patients (76% female). Mean ± SD age of onset of the disease was 18 ± 15 years. The mean duration of disease at baseline was 14 ± 15 years (**Table I**). Mean baseline SALT score was 86 ± 24%, and eyebrows/eyelashes were involved in 82% (14/17) of patients.

Mean tofacitinib treatment duration was 13 months (SD 5.8). The majority of patients were treated combining with oral minoxidil (65%, 11/17). Doses of oral minoxidil ranged between 0.5 and 1 mg/day for women (45% of the women received minoxidil, 5/11) and 2.5–5 mg/day for men (75% of the men received minoxidil, 3/4).

SALT score improved over 1 year of treatment (Fig. S1, $p = 0.02$) from 86 ± 24 to 26 ± 36 (**Fig. 1**). Stratified analyses were performed for sex, age of onset of the disease (<15 vs >15 years), co-treatment with oral minoxidil and evolution time of the disease at the start of the treatment with tofacitinib (<5 vs >5 years of evolution). No difference was found in SALT evolution over time between these groups ($p > 0.50$). At 12 months, 58% of the patients

Table I. Sociodemographic and clinical features of the study sample and characteristics of tofacitinib treatment

Variables	All patients ($n = 17$)
Socio-demographic features	
Age, years, mean (SD)	32.58 (18.69)
Age of onset, years (SD)	18.35 (14.95)
Sex Male, % (*n*/N)	23.6 (4/17)
Female, % (*n*/N)	76.4 (13/17)
Evolution time of the disease, years (SD)	14.23 (14.92)
Previous treatments, (*n*/N)	
Topical corticosteroids	100 (17/17)
Intralesional steroids	60 (9/15)
Topical minoxidil	93.3 (14/15)
Topical anthralin	41.2 (7/17)
Oral corticosteroids	100 (17/17)
Immunosuppressive agents	58.8 (10/17)
Comorbidities, (*n*/N)	
Hypothyroidism,	17.6 (3/17)
Coeliac disease	0 (0/17)
Type 1 diabetes mellitus	0 (0/17)
Other immune-mediated diseases	40 (6/15)
Severity of the disease	
Basal SALT score, mean (SD)	86.25 (24.32)
Eyebrows/eyelashes involvement, % (*n*/N)	82.4 (14/17)
Treatment characteristics	
Tofacitinib dose, % (*n*/N)	
High dose (5 mg/12 h)	94.1 (16/17)
Low dose (5 mg/24 hI	5.9 (1/17)
Treatment time (months)	13 (SD 5.76)
Cumulative dose of tofacitinib (mg), mean (SD)	3,787.5 (1,806)
Oral minoxidil co-treatment, % (*n*/N)	64.70 (11/17)

SD: standard deviation; SALT: Severity of Alopecia Tool.

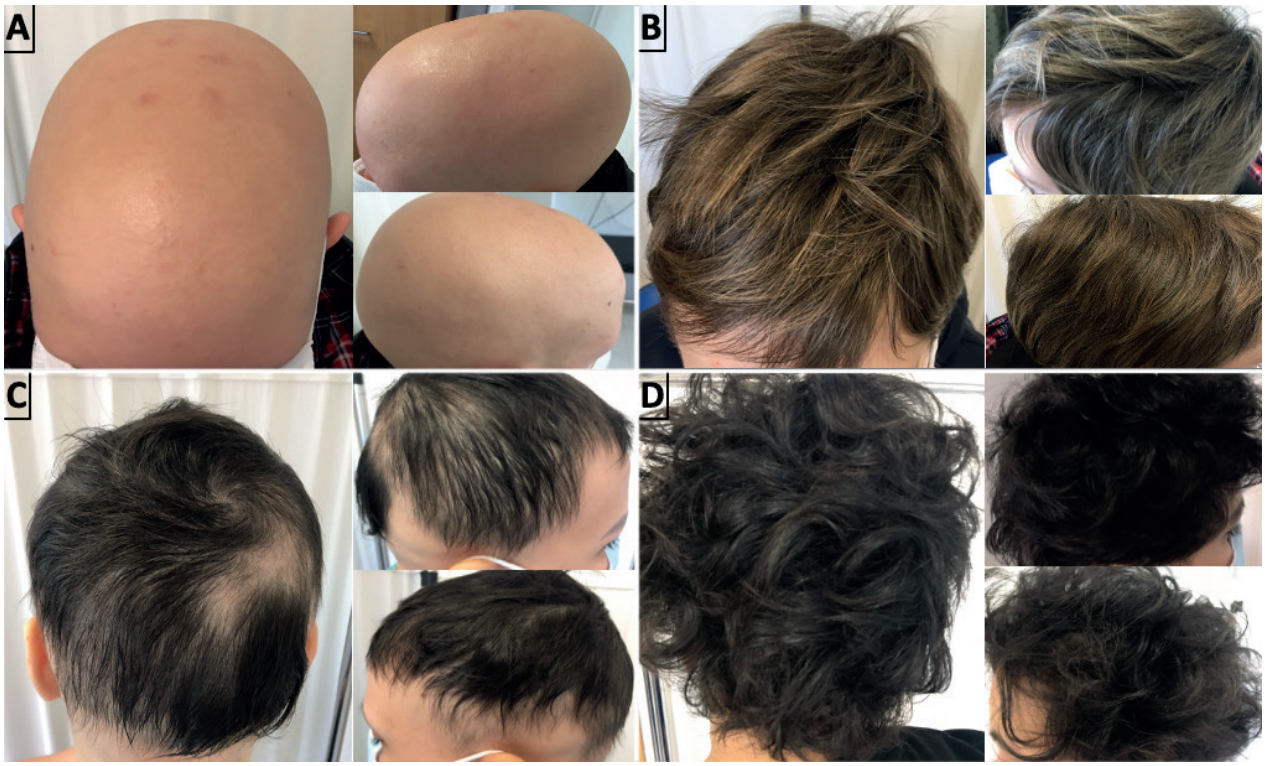

Fig. 1. Examples of 2 patients who had a good response with tofacitinib treatment. Pre- (a, c), and post-treatment (b, d) photographs show great improvement after treatment.

had a SALT score reduction of 75% compared with baseline (Fig. S2).

Four percent (7/17) of patients experienced an adverse effect related to tofacitinib treatment. None of the adverse effects were life-threatening. These included: urinary or digestive infections, 25% (4/17); herpes zoster 12% (2/17), and acneiform rash, 6% (1/17). Once infections were diagnosed, tofacitinib treatment was discontinued until patients were recovered. All patients recovered from treatment side-effects without any complications. The daily dose of tofacitinib and cumulative doses were not related to the appearance of side-effects ($p > 0.30$).

DISCUSSION

Oral tofacitinib is an effective treatment for severe cases of AA that failed to respond to other therapies, leading to progressive and high rates of SALT reduction up to 12 months. The response rates may be higher than those achieved by corticosteroids (3). Moreover, effectiveness does not appear to be related to sex, age of onset, duration of the disease, or treatment combination with oral minoxidil. Side-effects appear to be frequent but mild, and do not lead to definite treatment interruption in most cases.

Tofacitinib is a JAK1/JAK3 inhibitor, which has been used in the treatment of many inflammatory conditions (5, 11). Response rates obtained in the present study are promising, with 75% achieving SALT-50 response, and 58% SALT-75 response at 12 months. These data show slightly better response rates than previous studies (8). Side-effects of the treatment include haematological disturbances; elevation of hepatic enzymes and cholesterol; infections, including herpes zoster and tuberculosis reactivations; venous thromboembolism; and an increase in the appearance of solid organ and haematological neoplasms, including non-melanoma skin cancer (12). Acneiform rash, which is present in the current study, has also been described (8). These side-effects are often mild and do not require definitive treatment interruption. In the current study, urinary and digestive infections, and reactivation of herpes zoster were the most common side-effects.

Despite some reports that oral minoxidil may be effective in AA, there is a lack of firm evidence to support its use (14). In the patients in the current study, co-treatment did not appear to be related to a better improvement in SALT scores over time, although the doses used were lower than those used in previous reports. Until better evidence is described, the recommendation to treat these patients with oral minoxidil should be made on an individual basis.

Other JAKi, which have been reported for the treatment of AA include ruxolitinib (5), and baricitinib (15). Both drugs are JAK1/JAK2 inhibitors and seem to achieve improvements in SALT score.

In conclusion, tofacitinib seems to be an effective therapeutic approach for patients with severe AA refractory to topical and systemic therapies. Most common side-effects are infections, which are more often mild

and do not lead to definitive treatment interruption.

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This study has been approved by the Institutional Review Board of the Hospital Universitario Virgen de las Nieves.

The authors have no conflicts of interest to declare.

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