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Clinical trial

Sublingual tofacitinib for alopecia areata: a roll-over pilot clinical trial and analysis of pharmacokinetics

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Abstract

Tofacitinib is a JAK1/3 inhibitor used off-label to treat alopecia areata (AA). Oral tofacitinib undergoes extensive hepatic metabolism and has numerous drug interactions and a half-life of 3 hours necessitating twice daily dosing. Sublingual delivery bypasses hepatic first-pass metabolism, which may provide pharmacokinetic benefits and reduce gastrointestinal side effects. We investigate sublingual tofacitinib as a novel form of administration in a cohort of treatment-resistant patients. The objective of this work is to assess the efficacy and pharmacokinetics of sublingual tofacitinib in moderate-to-severe AA patients. An open-label, roll-over pilot clinical trial was conducted. Participants were recruited from a preceding trial. All responders (≥50% reduction in Severity of Alopecia Tool [SALT] score, SALT50) in the preceding trial continued on the same treatment (cyclosporine/placebo), whereas nonresponders rolled over to receive open-label sublingual tofacitinib 5 mg twice daily for 12 weeks. Treatment response as reduction in SALT score after 12 weeks (low: 15–29%, medium: 30–49%, good: 50–75%, and high grade: 75–100%) was measured. Pharmacokinetics was analyzed using liquid chromatography tandem mass spectrometry. Eighteen participants completed the trial. Total treatment response to tofacitinib was 37.5%. SALT50 was achieved in 12.5%. The mean improvement in SALT score was 15.57%. Mean maximum plasma concentration was 43.18 ng/ml occurring after 1 hour. Elimination half-life is estimated to be up to 11 hours. An estimated half-life of up to 11 hours may be achieved with sublingual tofacitinib, which is significantly longer than the oral form and may facilitate daily dosing. Larger clinical trials are required to further characterize its pharmacokinetics and efficacy.

Introduction

Alopecia areata (AA) is a common, relapsing and remitting, autoimmune hair loss condition. Disease spectrum varies from a single patch to multifocal patches to loss of entire scalp hair (known as alopecia totalis [AT]), and to complete loss of all scalp and body hair, known as alopecia universalis (AU). There is an inverse association between disease duration and likelihood for spontaneous regrowth; patients with a patch of AA for greater than 12 months have a 45% risk of progressing to AT/AU.[1] AA is associated with significant psychological morbidity. Estimated mean health utility, from a scale of 0 (death) to 1 (full health quality-adjusted life years), is calculated to be 0.748 for Australian AA patients.[2]

Current therapies are suboptimal. Prednisolone, although effective, has significant side effects, and conjunctive use of steroid-sparing agents, including cyclosporine, methotrexate, and azathioprine, only allows 35.9% of patients to wean off prednisolone entirely at 12 months.[3] Of the steroid-sparing agents, only one placebo-controlled randomized trial has

investigated the efficacy of cyclosporine monotherapy in the treatment of AA, with an efficacy of up to 31.3%; however, this did not reach statistical significance due to small sample size.[4] Uncontrolled case series demonstrate the efficacy of monotherapy methotrexate and azathioprine to be between 38 and 43%.[3] Ultimately, systematic reviews identify no reliable evidence-based treatments for chronic AA.[5]

Many of the inflammatory responses involved in the pathogenesis of AA share common signaling transduction via the Janus kinase–signal transducer and activator of transcription proteins (JAK-STAT) pathway, in which proinflammatory cytokines such as interferon gamma (IFN-γ) and interleukin-15 (IL-15) activate JAK. Blockade of this pathway through JAK inhibitors is a target of interest for new treatments.

Specifically, tofacitinib – a JAK1/3 inhibitor – has been investigated in multiple studies, with a meta-analysis of six clinical trials and eight observational studies suggesting an overall 54.0% good/complete hair regrowth rate.[6] Dose and treatment duration were important variables: 66.7% compared with 31.8% of participants achieved response on >5 mg twice daily dosing versus ≤5 mg twice daily dosing, respectively, and this result was the same for duration >6 months versus ≤6 months.[6] Subgroup analyses demonstrated the good/complete response rate was lower in clinical trials, 34.5%, compared with observational studies, 56.6%.[6]

Notably, oral tofacitinib undergoes extensive hepatic metabolism, has numerous drug interactions, and has an elimination half-life of 3 hours necessitating twice daily dosing. Adverse events include an increased risk of infections, lymphoma, thromboembolism, liver steatosis, gastrointestinal perforation, dyspepsia, and diverticulitis.[6–8] No studies have investigated sublingual tofacitinib, which may provide benefit as the sublingual form bypasses hepatic first-pass metabolism, circumvents gastrointestinal side effects, and may reduce drug interactions orchestrated through hepatic CYP450 enzyme metabolism. In this study, we report a pilot trial to evaluate the efficacy, pharmacokinetics, and adverse events of sublingual tofacitinib in patients with moderate-to-severe, treatment-resistant AA.

Methods

We conducted an open-label, roll-over clinical trial. Adults aged 18–65 years with moderate-to-severe AA who completed an initial trial were recruited in person at the final visit of the initial trial to take part in this pilot study[9] (Fig. 1). Responders (minimum 50% reduction in Severity of Alopecia Tool [SALT] score, i.e., SALT50) to treatment in the initial trial were allocated to continue a 12-week extension of the same blinded treatment (cyclosporine/placebo), whereas nonresponders were allocated to receive open-label privately compounded sublingual tofacitinib 5 mg twice daily for 12 weeks after a 4-week washout period. Exclusion criteria included pregnancy, lactation, nonadherence to prescribed contraception; use of hair-promoting treatments; tofacitinib use within 12 weeks; history of lymphoproliferative disorders, HIV, tuberculosis, hepatitis B, or hepatitis C; active herpes simplex infection; and hypersensitivity to study medication.

Monthly assessments included SALT score, eyelash and eyebrow scales (categorical rating from 0, none, to 3, normal), quality-of-life (QOL) questionnaires (Alopecia Areata Symptom Impact Scale, AASIS, and Assessment of Quality of Life-8D, AQoL-8D), and adverse event monitoring. Adverse events were monitored through monthly blood biochemistry, together with patient self-reporting of symptoms and a thorough examination.

The SALT score is an internationally recognized severity score representing total percentage hair loss through a weighted summation of left, right, superior, and posterior scalp hair loss.[10] The AASIS is a disease-specific instrument, used to characterize QOL impacted by AA,[11] whereas the AQoL-8D is a generic instrument, which enables QOL comparison across diseases in Australia.[12]

Blood samples were collected from tofacitinib-arm participants at baseline and after 12 weeks at 0, 0.5, 1, 3, and 24 hours. Samples were centrifuged and the resultant plasma analyzed using liquid chromatography tandem mass spectrometry method to determine tofacitinib plasma concentrations. The maximum observed plasma concentration (C_{max}) and time to C_{max} (t_{max}) was calculated. Half-life was estimated through linear extrapolation.

Statistical analyses were performed using Stata 12 software. Descriptive statistics were summarized using means and standard deviations. Mann–Whitney *U* tests for nonnormally distributed continuous data and chi-squared tests for categorical data were performed to compare groups. Statistical significance was defined as $P < 0.05$. As this was a pilot study, the efficacy data presented may help calculate future sample sizes required for statistical significance.

Ethical approval was received from Bellberry Human Research Ethics Committee E (EC00450).

Results

Twenty participants enrolled; two received continuation treatment (cyclosporine), and 18 received tofacitinib. The majority of tofacitinib participants had AT/AU (72.22%), with 100% or some body hair loss (83.33%) (Table 1).

Showing some response to sublingual tofacitinib were 37.5% of participants, and 12.5% achieved SALT50 (Table 2). Mean reduction from baseline of SALT score was 15.57%.

Achieving at least a one grade improvement in eyelash assessment scale were 37.5% of participants, and 50% achieved at least a one grade improvement in eyebrow assessment scale. The two participants on cyclosporine did not achieve significant incremental improvement at 24 weeks compared to the initial 12 weeks. There were no serious adverse events.

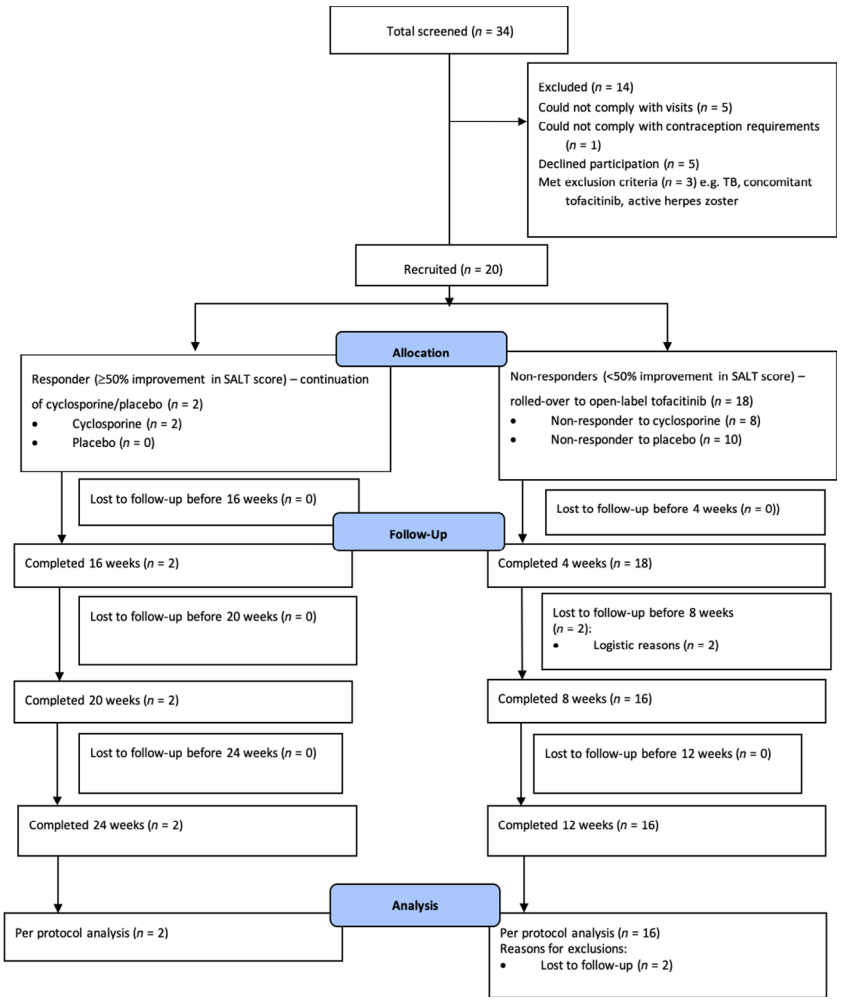

Figure 1 Flow diagram of allocation, follow-up, and analysis of participants

Seventy-two plasma samples were analyzed. Mean C_{max} was 43.18 ng/ml. t_{max} was 1 hour. The approximate half-life of sublingual tofacitinib was 11 hours, albeit limited by a lack of time-point data between 3 and 24 hours.

Discussion

This is the first study to investigate sublingual tofacitinib. Only 12.5% of participants achieved SALT50, which is lower compared with meta-analysis data that suggests a 34.5% response rate to oral tofacitinib.[6] The lower response rates seen in this clinical trial may represent either a lower efficacy of the sublingual tofacitinib compared with oral or reflect difficulties treating a cohort of severe, treatment-resistant disease. The tofacitinib group had a mean duration of current episode of AA of 7.79 years and mean scalp hair loss at baseline of 86.01%, and more than 70% of participants had AT/AU with more than 50% with duration greater than 2 years. The cohorts in current trials generally have a mean duration of current episode of AA of 5 years and 50% of participants with AT/AU.[8,13]

Optimal dosage of tofacitinib is important, given the toxicities associated with higher doses, particularly pulmonary embolism. In the two clinical trials reported for oral tofacitinib, one found a good response at 5 mg twice daily in 32% of participants,[8] whereas the other demonstrated limited response despite prolonged treatment and required dose escalation to 10 mg twice daily.[13] Currently, due to safety concerns, a dosage of 10 mg twice daily is not recommended for either rheumatoid arthritis or psoriatic arthritis.[14] Our pharmacokinetics analysis suggests sublingual tofacitinib may have a substantially longer half-life of 11 hours, compared with a half-life of 3 hours for oral tofacitinib.[15–17] Sublingual tofacitinib may enable once-daily rather than twice-daily dosing. None of our participants received potent CYP3A4 inhibitors. Further pharmacokinetic studies are required to evaluate whether there remains substantial interaction with CYP3A4 drugs with sublingual administration. A further

Table 1 Baseline demographic and clinical characteristics of all randomized participants

	All (n = 20)	Continuation arm (n = 2)	Tofacitinib arm (n = 18)
Age (years)	44 (14.96)	34 (5)	45.11 (15.28)
Sex (female)	15 (75%)	1 (50%)	14 (77.78%)
Age at onset of first episode of AA (years)	26.75 (14.92)	18 (11)	27.72 (14.99)
Age at onset of current episode of AA (years)	37 (15.24)	32.5 (5.5)	37.50 (15.89)
Duration of current episode of AA (years)	7.13 (11.48)	1.25 (0.25)	7.79 (11.92)
Mean percentage scalp hair loss by SALT score at baseline (%)	81.59 (26.53)	41.75 (19.75)	86.01 (23.30)
Pattern of scalp hair loss, *n* (%)			
AT	6 (30%)	0 (0%)	6 (33.33%)
AU	8 (40%)	1 (50%)	7 (38.89%)
Patchy	6 (30%)	1 (50%)	5 (27.78%)
Body hair loss, *n* (%)			
100% loss	8 (40%)	1 (50%)	7 (38.89%)
No loss	3 (15%)	0 (0%)	3 (16.67%)
Some loss	9 (45%)	1 (50%)	8 (44.44%)
Nail involvement	10 (50%)	2 (100%)	8 (44.44%)
History of AT/AU at any time	16 (80%)	2 (100%)	14 (77.77%)
Duration of AT/AU, *n* (%)			
≤2 years	8 (50%)	2 (100%)	6 (42.89%)
>2 years	8 (50%)	0 (0%)	8 (57.14%)
Medical history, *n* (%)			
Atopy	6 (30%)	0 (0%)	6 (33.33%)
Endocrine	2 (10%)	0 (0%)	2 (11.11%)
Psychological illness	2 (10%)	0 (0%)	2 (11.11%)
Family history of AA	2 (10%)	0 (0%)	2 (11.11%)
Score of 0 (no eyelashes) on eyelash assessment scale	10 (50%)	0 (0%)	10 (55.56%)
Score of 0 (no eyebrows) on eyebrow assessment scale	11 (55%)	0 (0%)	11 (61.11%)

Data are means (SD) or numbers (%).
AA, alopecia areata; AT, alopecia totalis; AU, alopecia universalis.

Table 2 Summary of results for primary and secondary objectives

Endpoint	Tofacitinib group (n = 16)
Primary objective – efficacy of sublingual tofacitinib	
Mean reduction from baseline of SALT score after 12 weeks	15.57 (23.41)
Treatment response (reduction in SALT score after 12 weeks)	
Low grade respondents (15–29%)	3/16 (18.75%)
Medium grade respondents (30–49%)	1/16 (6.25%)
Good grade respondents (50–75%)	1/16 (6.25%)
High grade respondents (75–100%)	1/16 (6.25%)
Total participants showing some response	6/16 (37.5%)
Proportion of participants achieving at least 1 grade improvement in eyelash assessment scale after 12 weeks	6/16 (37.5%)
Proportion of participants achieving at least 1 grade improvement in eyebrow assessment scale after 12 weeks	8/16 (50%)
Secondary objective – quality-of-life measurements	
Mean change from baseline in Assessment of Quality of Life-8D[a] (AQoL-8D) score after 12 weeks (n = 13)	−0.0148 (0.0515)
Mean change from baseline in Alopecia Areata Symptom Impact Scale (AASIS) score after 12 weeks – Global Symptom Impact Score[b] (n = 14)	−0.1306 (0.1252)
Mean change from baseline in Alopecia Areata Symptom Impact Scale (AASIS) score after 12 weeks – Scalp Hair Loss Score[c] (n = 14)	−2.2142 (2.3916)
Secondary objective – pharmacokinetics	
Mean maximum plasma concentration (C_{max})	43.18 ng/ml
Time to mean maximum plasma concentration (t_{max})	1 h

Data are mean (standard deviation) or proportion (percentage).
[a]The AQoL-8D scale measures QOL on a scale from 0 (death) to 1 (full health), positive values reflect an improvement in QOL.
[b]The Global Symptom Impact Score measures all AA symptom impact on a scale of 0 (all symptoms not present) to 1 (all symptoms as bad as you can imagine), negative values reflect an improvement in symptom impact.
[c]The Scalp Hair Loss Score measures AA scalp hair loss from 0 (not present) to 10 (as bad as you can imagine), negative values reflect an improvement in scalp hair loss.

subgroup of interest would be those with hepatic impairment. In this 12-week clinical trial, we found no significant adverse events to sublingual tofacitinib. However, we note that a longer trial may be required to reveal these adverse events.

Tofacitinib is a selective inhibitor of JAK1 and JAK3 and blocks several important cytokines (IL-2, -4, -7, -9, -15, and -21) involved in lymphocyte activation, proliferation, and immune response. Further pharmacokinetic research with a greater number of time points is required to determine full area under the plasma concentration time curve (AUC) required to elucidate any differences in metabolism, excretion, and action that could explain lower sublingual response rates despite a similar maximum mean plasma concentration to oral tofacitinib.

Our results are limited by a small sample size. From these pilot study results, we may calculate that for a two-sided 5% significance level and power of 80%, a sample size of at least

100 participants per group is required, based on 12.5% achieving SALT50 in sublingual tofacitinib.

In conclusion, our study provides the relevant foundation for larger studies to confirm pharmacokinetics data and efficacy. We demonstrate potential efficacy of sublingual tofacitinib to treat moderate-to-severe AA as an alternative to oral administration. Further research is required to elucidate dose-dependent efficacy and safety of sublingual tofacitinib, characterize its drug interactions, and determine differences in AUC compared with oral tofacitinib.

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