An Open-Label Pilot Study to Evaluate the Efficacy of Tofacitinib in Moderate to Severe Patch-Type Alopecia Areata, Totalis, and Universalis

A. Jabbari[1,2], F. Sansaricq[1], J. Cerise[1], J.C. Chen[1], A. Bitterman[1], G. Ulerio[1], J. Borbon[1], R. Clynes[1,3,4,5], A.M. Christiano[1] and J. Mackay-Wiggan[1]

Alopecia areata (AA) is a common autoimmune disease with a lifetime risk of ~2%. In AA, the immune system targets the hair follicle, resulting in clinical hair loss. The prognosis of AA is unpredictable, and currently there is no definitive treatment. Our previous whole genome expression studies identified active immune circuits in AA lesions, including common γ-chain cytokine and IFN pathways. Because these pathways are mediated through JAK kinases, we prioritized clinical exploration of small molecule JAK inhibitors. In preclinical trials in mice, tofacitinib successfully prevented AA development and reversed established disease. In our tofacitinib trial in 12 patients with moderate to severe AA, 11 patients completed a full course of treatment with minimal adverse events. Following limited response to the initial dose (5 mg b.i.d.), the dose was escalated (10 mg b.i.d.) for nonresponding subjects. Eight of 12 patients demonstrated ≥50% hair regrowth, while three patients demonstrated <50% hair regrowth, as measured by Severity in Alopecia Tool scoring. One patient demonstrated no regrowth. Gene expression profiles and Alopecia Areata Disease Activity Index scores correlated with clinical response. Our open-label studies of ruxolitinib and tofacitinib have shown dramatic clinical responses in moderate to severe AA, providing strong rationale for larger clinical trials using JAK inhibitors in AA. ClinicalTrials.gov ID NCT02299297.

Journal of Investigative Dermatology (2018) ■, ■–■; doi:10.1016/j.jid.2018.01.032

INTRODUCTION

Alopecia areata (AA) is a common autoimmune disease with a lifetime risk of approximately 2%, affecting an estimated 5.3 million individuals in the United States (McMichael et al., 2007; Safavi et al., 1995). Persistent moderate to severe AA causes significant disfigurement and psychological distress to affected individuals (Colon et al., 1991). Clinical development of innovative therapies in AA has lagged far behind other autoimmune conditions.

AA results from an autoimmune attack on the hair follicles. Using comparative genomics of the transcriptional profiles of skin from both AA model mice and humans with AA, we found that cytotoxic CD8 (+) NKG2D (+) T cells are both necessary and sufficient for the induction of AA in mouse models of disease. On the basis of our preclinical findings (Xing et al., 2014), we initiated a phase 2 efficacy signal-seeking clinical trial in moderate to severe AA, assessing the clinical and immunopathological response to treatment with oral tofacitinib, a JAK1,3 inhibitor that also inhibits JAK2. Presently, tofacitinib is Food and Drug Administration–approved for the treatment of adult patients with moderate to severe rheumatoid arthritis and is under study for many other autoimmune conditions (Schwartz et al., 2016). Tofacitinib has been shown to prevent the onset of, and reverse, AA in the C3H-HeJ animal model of AA. Thus far, several studies have demonstrated clinical efficacy of oral tofacitinib in patients treated with AA (Jabbari et al., 2016) or alopecia universalis (AU) (Kennedy et al., 2016; Liu et al., 2017). In all reported cases, clinical response was achieved with minimal or no adverse events.

RESULTS

Primary Efficacy End Point

This study was an open-label, clinical trial to investigate tofacitinib 5 mg to 10 mg p.o. twice daily in the treatment of moderate to severe AA.

Eight of 12 patients met the study's primary efficacy end point of ≥50% hair regrowth from baseline as assessed by the Severity in Alopecia Tool (SALT) at the end of treatment. The duration of treatment ranged from 6 to 18 months, at the discretion of the investigator and dependent on the individual subject's response, as well as safety considerations. The

[1]Department of Dermatology, Columbia University, New York, New York, USA; [2]Department of Dermatology and Interdisciplinary Program in Immunology, University of Iowa, Iowa City, Iowa, USA; [3]Department of Genetics, Columbia University, New York, New York, USA; [4]Department of Pathology, Columbia University, New York, New York, USA; and [5]Department of Medicine, Columbia University, New York, New York, USA

Correspondence: Julian Mackay-Wiggan, Department of Dermatology, Columbia University, College of Physicians and Surgeons, Herbert Irving Pavilion, 161 Fort Washington Avenue, Room 1264, New York, New York 10032, USA. E-mail: jc299@columbia.edu

Abbreviations: AA, alopecia areata; ALADIN, Alopecia Areata Disease Activity Index; AT, alopecia totalis; AU, alopecia universalis; SALT, Severity in Alopecia Tool

Received 19 September 2017; revised 9 January 2018; accepted 26 January 2018; accepted manuscript published online 13 February 2018; corrected proof published online XXX

length of time from baseline for patients to reach the primary efficacy end point was, on average, 32 weeks, with the time period ranging from as little as 8 weeks to as much as 64 weeks (Figures 1 and 2, Table 1).

Four of the five patients with either alopecia totalis (AT) or AU achieved ≥50% response in hair regrowth. All patients who had reached the study's primary efficacy end point, with the exception of one patient, failed to respond to lower doses, in some cases despite prolonged treatment, but responded with onset of regrowth within 4 weeks of initiation of the higher dose of tofacitinib, at 10 mg b.i.d.

Secondary Efficacy Outcomes

As secondary end points, efficacy was measured by changes in hair regrowth as a continuous variable, as determined by physical examination and Canfield photography, as well as patient and physician global evaluation scores.

Global overall improvement in SALT score at end of treatment. Eleven of 12 patients attained a global overall improvement in SALT score at the end of treatment, with results ranging from 12.1% to 100% regrowth, with an average 56.8% regrowth. Baseline SALT scores for the 12 patients ranged from 46% to 100%, and at the end of treatment SALT scores ranged from 0% to 99%. The average baseline SALT score of 81.3% decreased to 40.8% at the end of treatment. Only one subject had no response to the study medication after 36 weeks of administration, having experienced a negligible decrease in SALT score, with approximately 1% hair regrowth that consisted of 0.5- to 1-mm depigmented fine terminal hairs throughout the scalp and facial area. Vellus hair growth was not used in SALT score calculations. No patients experienced worsening of AA from baseline at the time of treatment discontinuation, with 11 patients exhibiting varying degrees of hair regrowth.

Time to regrowth of scalp and body hair. Regrowth was seen in responders as soon as 4 weeks after the effective dose of study medication was initiated. All 12 patients experienced between 0 and <25% of hair regrowth by week 4, as assessed by Physician Global Assessment, a static evaluation of scalp regrowth rated as "worse," "same," or "improved." The degrees to which hair regrowth presented itself at 4 weeks were highly varied and individual responses ranged from <1% with the introduction of few fine terminal hairs to at most approximately 45% regrowth with depigmented and pigmented, terminal and fine terminal hairs. Three patients displayed mild shedding of scalp hair while on tofacitinib, but at end of treatment, remained improved compared to baseline.

All 12 enrolled patients exhibited varying degrees of body hair regrowth. Regrowth of body hair was documented as soon as 4 weeks after effective dose of study medication was initiated. Body hair regrowth was mixed, with some patients experiencing minimal to full facial hair regrowth, including eyelashes and eyebrows. Other areas of body hair regrowth noted in patients included the arms, legs, axillary, and groin area.

Durability of responses. To assess the durability of responses, patients who achieved 50% regrowth from baseline during the first 6 to 18 months were followed for an additional 6 months off treatment or until it was determined that relapse had occurred. Of the eight patients who achieved 50% regrowth, one patient dropped out of the observation period in order to continue the medication outside of the study. Of the seven patients who were followed observationally, six patients exhibited variable hair shedding after completion of the study treatment, with two patients showing initial signs of shedding approximately 3−4 weeks after end of treatment, and four patients showing initial signs of shedding approximately 8 weeks after end of treatment. Hair shedding was initially slight, but accelerated at 4−6 months off tofacitinib. The final patient did not exhibit any hair shedding throughout the observational period (24 weeks/6 months off tofacitinib). Excellent durability of response was seen in three of the eight responders, maintaining lower SALT scores compared to baseline SALT scores at nearly 24 weeks off tofacitinib. Four patients experienced worsening of AA compared to baseline at the conclusion of the study, at nearly 24 weeks off the study medication. Shedding of body hair coincided with the timeline of scalp hair loss.

Overall, 11 of the 12 patients who were initially enrolled in this study completed the intended 24 to 72 weeks of study treatment. One patient underwent early termination of the study treatment at week 12 due to experiencing hypertensive urgency as an adverse event.

Change in patient quality of life assessment. Change in patient quality of life assessment was compared from baseline to selected visits during the treatment period (weeks 12 and 24). Quality of life measures were based on changes in the Dermatology Life Quality Index (Basra et al., 2008). Seven of the 12 patients experienced a decrease in their Dermatology Life Quality Index score, as measured from baseline to week 24 (Supplementary Table S1 online). The mean baseline Dermatology Life Quality Index score of 6.5 ± 5 decreased to 5.2 ± 6.7 at 3 months of treatment and later increased to 6 ± 6.9 at the end of 6 months of treatment.

Differences in regrowth between patients with patch-type AA versus patients with AT or AU. At the end of treatment, the five subjects who had either AT or AU had experienced hair regrowth ranging from 1.0% to 84%, with an average of 52.2% regrowth. This is in comparison to subjects with moderate to severe patchy AA who, at the end of treatment, experienced hair regrowth ranging from 12.1% to 100%, with an average 52.1% regrowth. Overall, patients with patch-type AA or AT or AU had, on average, very similar percentage hair regrowth at the end of study treatment. Given the small sample of these patients, it is not known if the observation of similar regrowth rates among AA, AT, and AU patients will continue to hold in future studies.

Biomarker and Clinical Correlative Studies

Gene expression profiling was performed on skin biopsies taken at baseline and up to 24 weeks of treatment, with additional optional biopsies performed if indicated by clinical considerations.

We applied both naïve and supervised clustering to this data set in order to assess two features: the overall molecular effect of tofacitinib treatment on patient samples and the concordant molecular response of the disease. The former was assessed by an unbiased, unsupervised differential