Tofacitinib for the treatment of severe alopecia areata and variants: A study of 90 patients

Lucy Y. Liu, BA,[a] Brittany G. Craiglow, MD,[b,c] Feng Dai, PhD, MS,[d] and Brett A. King, MD, PhD[b]
New Haven, Connecticut

Background: Alopecia areata (AA) is a common autoimmune disorder. There are no reliably effective therapies for AA.

Objective: We sought to evaluate the safety and efficacy of the Janus kinase 1/3 inhibitor, tofacitinib, in a series of patients over an extended period of time.

Methods: This is a retrospective study of patients age 18 years or older with AA with at least 40% scalp hair loss treated with tofacitinib. The primary end point was the percent change in Severity of Alopecia Tool (SALT) score during treatment.

Results: Ninety patients met inclusion criteria. Of 65 potential responders to therapy, defined as those with alopecia totalis or alopecia universalis with duration of current episode of disease of 10 years or less or alopecia areata, 77% achieved a clinical response, with 58% of patients achieving greater than 50% change in SALT score over 4 to 18 months of treatment. Patients with AA experienced a higher percent change in SALT score than did patients with alopecia totalis or alopecia universalis (81.9% vs 59.0%). Tofacitinib was well tolerated, and there were no serious adverse events.

Limitations: The retrospective nature of the data, the relatively small number of patients, and lack of a control group are limitations.

Conclusion: Tofacitinib should be considered for the treatment of severe AA, alopecia totalis, and alopecia universalis; tofacitinib dose response will be better defined by randomized controlled trials. (J Am Acad Dermatol 2017;76:22-8.)

Key words: alopecia areata; Janus kinase; tofacitinib.

Alopecia areata (AA) is a common autoimmune disorder that affects both children and adults, with an estimated lifetime risk of 1.7%.[1] Variants of AA include alopecia totalis (AT), loss of all scalp hair, and alopecia universalis (AU), loss of all body hair. Current medical therapies for AA are not reliably effective, particularly for severe disease.[2]

Recent advances in the understanding of the pathogenesis of AA have yielded Janus kinase (JAK) inhibitors as a promising novel therapy.[3] In a murine model of AA, natural killer gene 2D–expressing

Abbreviations used:

AA:	alopecia areata
AT:	alopecia totalis
AU:	alopecia universalis
JAK:	Janus kinase
SALT:	Severity of Alopecia Tool

From the School of Medicine,[a] Departments of Dermatology[b] and Pediatrics,[c] and Center for Analytical Sciences,[d] Yale University.
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Reprint requests: Brett A. King, MD, PhD, Department of Dermatology, School of Medicine, Yale University, PO Box 208059, New Haven, CT 06520. E-mail: brett.king@yale.edu.
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$CD8^+$ T cells were shown to be central in AA, causing up-regulation of interleukin-15 in hair follicles and ultimately production of interferon-γ, which targets the hair follicle for attack. As downstream regulators of interferon-γ and interleukin-15, JAK inhibitors have been shown to eliminate the interferon signature and reverse disease.[3] Several recent case reports have demonstrated efficacy of JAK inhibitors for the treatment of AA, including ruxolitinib (JAK 1/2) in both oral[3] and topical formulations,[4] tofacitinib (JAK 1/3),[5] and baricitinib (JAK 1/2).[6] An open-label clinical trial involving 66 patients treated for 3 months with tofacitinib showed promising results,[7] but the long-term benefit of tofacitinib has not been evaluated. In this retrospective study of 90 patients, we assess the long-term efficacy of tofacitinib for the treatment of AA and variants.

CAPSULE SUMMARY

- Short-term treatment with tofacitinib has shown efficacy for alopecia areata, but long-term data are lacking.
- In this series, long-term treatment of alopecia areata with tofacitinib was effective and well tolerated.
- Tofacitinib should be considered for the treatment of alopecia areata.

METHODS

We identified records of all patients with AA, AT, or AU who were evaluated at a tertiary care center clinic between July 2014 and October 2015; all data were updated through March 2016. Inclusion criteria for this study included patients age 18 years or older, a clinical diagnosis of AA with at least 40% scalp hair loss, AT, or AU (defined as scalp hair loss of ≥90%), stable or worsening disease for 6 months or longer, and treatment with tofacitinib for 4 months or longer. Clinical and demographic information for each patient was recorded, including age, gender, age of disease onset, duration of current episode of disease, family history, and AA severity as assessed by the Severity of Alopecia Tool (SALT).[8]

Before initiating treatment with tofacitinib, all patients had baseline laboratory evaluation that included complete blood cell count with differential, comprehensive metabolic panel, fasting lipid panel (total cholesterol, high-density lipoprotein, low density-lipoprotein, triglycerides), QuantiFERON-TB Gold (Cellestis Limited, Melbourne, Australia), serum human chorionic gonadotropin (in women of childbearing age), and screening for HIV and hepatitis B and C viruses. Photographs were taken before treatment was initiated and at subsequent clinic visits. These photographic data were used to assess disease severity and response to therapy. Efficacy was evaluated using the SALT score,[8] a validated tool that quantifies percent scalp hair loss. A SALT score of 0 indicates no hair loss; a SALT score of 100 indicates complete absence of hair. SALT scores were corroborated by 2 authors independently (L. Y. L. and B. A. K.), with average absolute difference of 3 and percent difference of 4%. Subsequently, a percent change in SALT score was calculated by dividing the absolute change in SALT score between initiation of treatment and last evaluation during treatment by the initial SALT score. Percent change in SALT score of 100% indicates complete regrowth, whereas 0% indicates no regrowth. Percent change in SALT score was used in all analyses. Safety was assessed with complete blood cell count with differential, complete metabolic panel, fasting lipid panel, physical examination, and review of systems.

Outcomes

The primary end point, called the latest percent change in SALT score, was the percent change in SALT score between the initial visit (before treatment) and the most recent visit while taking tofacitinib. Treatment duration was stratified in 3-month periods (4-6, 7-9, 10-12, 13-15, and 16-18 months), as timing of SALT scores during treatment varied based on when patients were seen in follow-up. Clinical response to tofacitinib was defined as greater than 5% change in SALT score. Complete clinical response was defined as greater than 90% change in SALT score. Because of the similar clinical phenotype of AT and AU and because there were only 2 patients with AT, subtypes were categorized into 2 groups: AA and AT/AU.

Statistical analysis

Descriptive statistics were used to summarize the data. Because of the non-normality of clinical response data, median and interquartile ranges are reported with percent change in SALT scores instead of absolute ranges.

The comparisons of different groups were performed using the Wilcoxon rank sum test. The Spearman rank correlation coefficient was computed to quantify the associations between duration of current episode of AT/AU and latest percent change in SALT score and between age and latest percent change in SALT score. All statistical analyses were performed with the statistical software SAS, Version 9.4 (SAS Institute, Cary, NC). A 2-sided *P* value of less than .05 was considered statistically significant. No

Table I. Baseline characteristics of patients with alopecia areata, alopecia totalis, or alopecia universalis (N = 90)

Age, y, median (range)	34.5 (18-70)
Sex, n (%)	
Female	50 (55.6)
Male	40 (44.4)
Duration of disease, y, median (range)	18 (2-54)
Duration of current episode of AT or AU, y, median (range)	4 (0-39)
AA subtype, n (%)	
Areata	13 (14.4)
Totalis	2 (2.2)
Universalis	75 (83.3)
Autoimmune comorbidities, n (%)	
Atopic dermatitis	23 (25.6)
Allergic rhinitis	4 (4.4)
Asthma	8 (8.9)
Thyroid disease	19 (21.1)
Vitiligo	9 (10.0)
Psoriasis	4 (4.4)
Rheumatoid arthritis	4 (4.4)
HLA-B27 spondylarthropathies	2 (2.2)
Family history of AA, n (%)	22 (24.4)
Family history of autoimmune disease, n (%)	52 (57.8)

AA, Alopecia areata; *AT*, alopecia totalis; *AU*, alopecia universalis.

formal adjustment to multiplicity was applied because of the exploratory nature of this study.

Study oversight

This study was approved by the Yale University Human Investigation Committee.

RESULTS

Patient characteristics

Of 237 patients evaluated with AA, AT, or AU, 90 patients met inclusion criteria. There were 40 men (44.4%) and 50 women (55.6%), with a median age at time of treatment of 34.5 years. Age of onset of AA ranged from 1.5 to 65 years, with disease duration of 2 to 54 years. Eighty-six percent of patients had AT or AU, with 36.4% of them developing AT or AU within 12 months of the first episode of AA. In all, 47 patients (52.2%) had autoimmune comorbidities, including atopic dermatitis, vitiligo, psoriasis, and thyroid disease. In addition, 24.4% of patients reported a family history of AA, and 57.8% reported a family history of other autoimmune diseases (Table I). At the time of study conclusion, 78 of 90 patients (86.7%) continued to take tofacitinib and, of the potential responders, 60 of 65 (92.3%) continued to take tofacitinib (vide infra). Three patients discontinued because of insurance denial of coverage. Eight patients discontinued because of lack of efficacy after a median duration of treatment of 7.5 months. One patient, who was responding well to tofacitinib, switched to ruxolitinib for financial reasons.

Table II. Potential responders, defined as patients with either alopecia totalis or alopecia universalis with duration of current episode of disease 10 years or less or alopecia areata (N = 65)

Age, y, median (range)	32 (18-69)
Sex, n (%)	
Female	32 (49.2)
Male	33 (50.8)
Duration of disease, y, median (range)	15 (2-45)
Duration of current episode of AT or AU, y, median (range)	2.5 (0-10)
Standard monotherapy group Tofacitinib 5 mg BID, n (%)	28 (43.1)
Adjuvant therapy group, n (%)	37 (56.9)
Tofacitinib >5 mg BID, n (%)	19 (29.2)
Tofacitinib 5 mg BID plus prednisone, n (%)	9 (13.8)
Tofacitinib >5 mg BID plus prednisone, n (%)	9 (13.8)
Duration of treatment, mo, median (range)	12 (4-18)
Spontaneous relapse, n (%)	5 (7.7)
Relapse on tapered dose, n (%)	3 (4.6)
% change in SALT score, median (IQR)	64.7 (10.0-88.0)
Taking tofacitinib at study conclusion, n (%)	60 (92.3)

AT, Alopecia totalis; *AU*, alopecia universalis; *BID*, twice a day; *IQR*, interquartile range; *SALT*, Severity of Alopecia Tool.

Potential responders to tofacitinib

Analysis of response rates yielded a critical period of greater than 10 years duration of current episode of AT or AU to be the point at which patients were much less likely to respond to treatment. This critical period was the duration of current episode of AT or AU for which 68% or more of patients experienced no response to tofacitinib (percent change in SALT score of ≤5%). Potential responders were thus defined as patients with AT or AU whose duration of current episode of disease was 10 years or less or patients with AA. Twenty-five patients were excluded from the analysis of potential responders based on duration of current episode of AT or AU greater than 10 years; notably, 8 patients in this group showed a clinical response, with a median percent change in SALT score of 39.7% over a median of 14 months of treatment.

Table II describes the clinical and treatment profiles of potential responders, including duration of treatment, treatment regimen, subtypes, and sex.

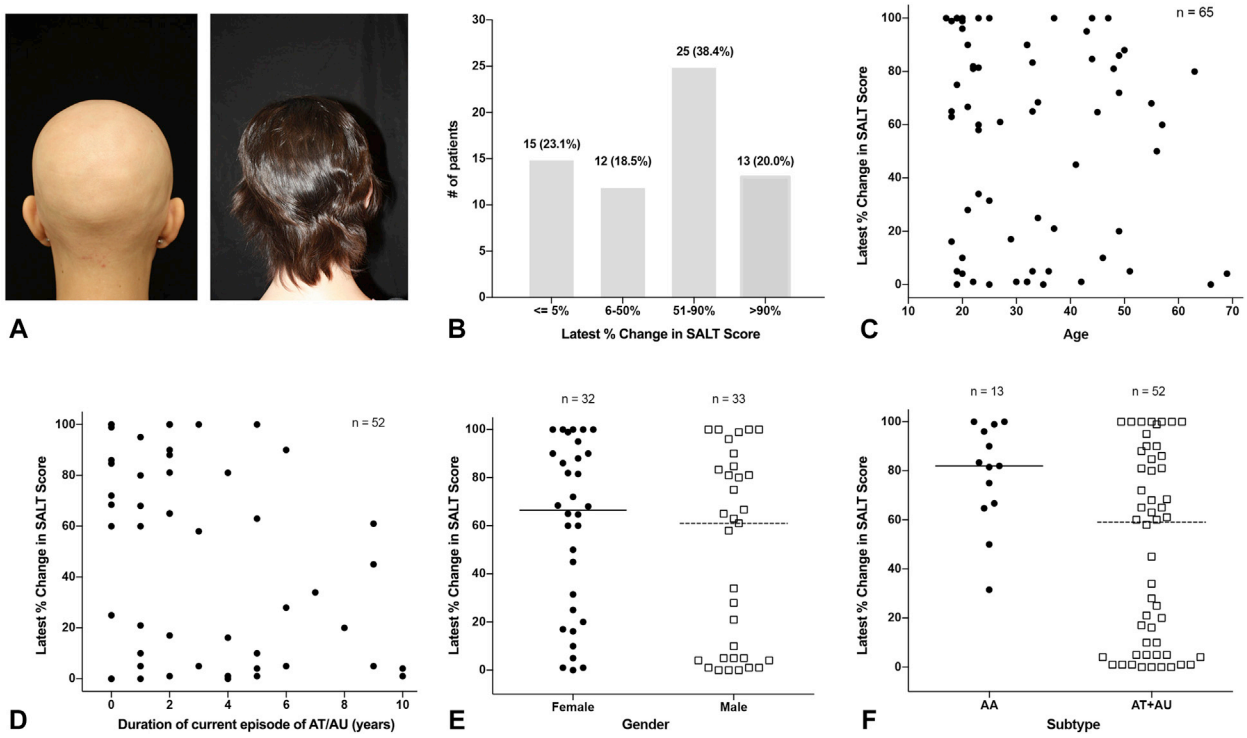

Fig 1. Clinical response to tofacitinib and its association with clinical variables. **A**, Photograph of a patient whose initial Severity of Alopecia Tool (*SALT*) score was 100 and whose latest SALT score was 0 (latest percent change in SALT score = 100%). **B**, Distribution of latest percent change in SALT score for potential responders (n = 65): 15 (23.1%) were nonresponders with a percent change in SALT score ≤5%, 12 (18.5%) had a moderate response of 6%-50%, 25 (38.4%) had an intermediate response of 51%-90%, and 13 (20.0%) had a complete response of >90%. **C**, There was no significant correlation between patient age and latest percent change in SALT score (Spearman rank $\rho = -0.14$, $P = .27$). **D**, There was a statistically significant negative correlation between duration of current episode of alopecia totalis (*AT*)/alopecia universalis (*AU*) and latest percent change in SALT score (n = 52, Spearman $\rho = -0.28$, $P = .048$). **E**, There was no statistically significant difference in the latest percent change in SALT score between men and women (median [interquartile range]: 61.0% [5.0-83.3] in men versus 66.5% [22.5-90.0] in women, $P = .25$). **F**, There was a statistically significant difference in the median latest percent change in SALT score between subtypes (median [interquartile range]: 81.9% [66.7-96.0] for alopecia areata [*AA*] vs 59.0% [5.0-85.4] for AT/AU, $P = .015$). Lines indicate median values.

Treatment, efficacy, and safety

All patients except for 3 received tofacitinib 5 mg twice daily monotherapy (standard monotherapy) for the first 2 to 3 months of treatment. Based on the presence or absence of hair regrowth at 2 to 3 months or a later time (if regrowth had plateaued), standard monotherapy was continued or adjuvant therapy was begun. Adjuvant therapy included either tofacitinib 5 mg twice daily plus prednisone or higher-dose tofacitinib up to 10 mg twice daily with or without prednisone; when used, the dose of prednisone was 300 mg once monthly for 3 doses (pulsed prednisone) except in a single patient taking prednisone 10 mg daily for arthropathy (started prior to tofacitinib). The 3 patients who did not receive standard monotherapy for the first 3 months of treatment were treated with tofacitinib 5 mg twice daily plus pulsed prednisone during this time. Of potential responders, 28 patients (43.1%) received standard monotherapy and 37 (56.9%) received adjuvant therapy (Table II).

Treatment response was assessed based on 4 categories: complete response (>90% change in latest SALT score), intermediate response (51%-90% change), moderate response (6%-50% change), and nonresponse (≤5% change).

The clinical response rate (those who achieved moderate, intermediate, or complete response) was 77% for all patients. Thirteen patients (20.0%) were complete responders with a median duration of 15 months of treatment; Fig 1, *A*, shows

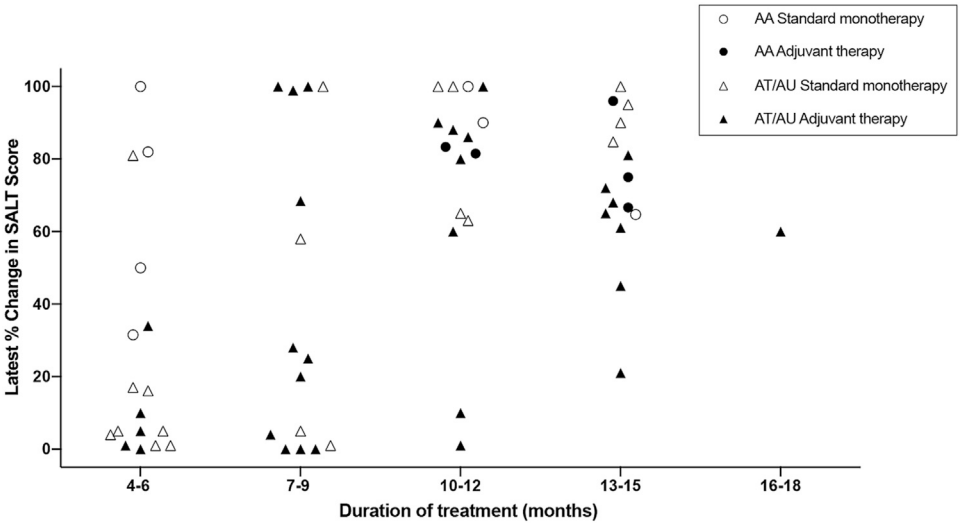

Fig 2. Latest percent change in SALT score is shown with subtypes and treatment regimen at different time periods. *AA*, Alopecia areata; *AT*, alopecia totalis; *AU*, alopecia universalis.

a patient who achieved 100% change in SALT score. Twenty-five patients (38.4%) were intermediate responders (median 14 months of treatment), 12 patients (18.5%) were moderate responders (median 11 months of treatment), and 15 patients (23.1%) were nonresponders (median 7 months of treatment) (Fig 1, *B*).

We found no statistically significant correlation between patient age and latest percent change in SALT score (Spearman $\rho = -0.14$, $P = .27$) (Fig 1, *C*). There was a statistically significant negative correlation between duration of current episode of disease and latest percent change in SALT score in patients with AT/AU (n = 52, Spearman $\rho = -0.28$, $P = .048$) (Fig 1, *D*). There was no significant difference between men and women in latest percent change in SALT score (median [interquartile range]: 61.0% [5.0-83.3] vs 66.5% [22.5-90.0], $P = .25$) (Fig 1, *E*). AA subtypes (n = 13) had a significantly higher percent change in SALT score than 52 patients with AT/AU (median [interquartile range]: 81.9% [66.7-96.0] vs 59.0% [5.0-85.4], $P = .015$) (Fig 1, *F*).

The latest percent change in SALT scores and the time periods at which they occurred in potential responders are shown in Fig 2. Note that this does not represent the time trajectories of hair regrowth on tofacitinib, which was not evaluated in this study.

Adverse events

There were no serious adverse events over a median duration of 12 months of treatment (Table III). Upper respiratory infections were the most commonly reported adverse event at 28.9%. Other infections included urinary tract infections and tonsillitis (reported by 3.3% and 2.2%, respectively). Additional common adverse events reported include headache (14.4%), acne (7.8%), and fatigue (6.7%). One patient, who was overweight at the time of starting tofacitinib and had baseline elevated aspartate aminotransferase (53 U/L, normal 10-40 U/L) and alanine aminotransferase (93 U/L, normal 9-46 U/L), experienced further elevations of aspartate aminotransferase (71 U/L) and alanine aminotransferase (129 U/L) during the initial 4 months of treatment; subsequently, in the context of weight loss (and while taking tofacitinib), his aspartate aminotransferase and alanine aminotransferase returned to the normal range. One patient developed leukopenia, defined as white blood cell count value less than 3700 U/μL, while on tofacitinib therapy; the patient's lowest white blood cell count, 3500 U/μL, increased into the normal range 6 months later without discontinuing treatment. Fifteen patients developed elevations in low-density lipoprotein with an average increase of 32.2 mg/dL. These elevations resolved in 3 patients, and the remaining 12 had stably elevated low-density lipoprotein during treatment.

DISCUSSION

The results of this study demonstrate that tofacitinib produces hair regrowth in severe AA, AT, and AU. Clinical response was achieved by 77% of patients, with 58% of patients achieving intermediate or complete response over 4 to 18 months of treatment. Considering that the majority of the patients in this study had AT or AU, the most severe forms of AA, the results are particularly noteworthy. The concomitant use of pulsed prednisone may be beneficial for patients who do not demonstrate a

Table III. Adverse events in patients taking tofacitinib (N = 90)

Infections	N (%)
URI	26 (28.9)
UTI	3 (3.3)
Tonsillitis	2 (2.2)
Varicella Zoster	2 (2.2)
Bronchitis	1 (1.1)
Conjunctivitis	1 (1.1)
Opportunistic infections	0 (0.0)
Tuberculosis	0 (0.0)
Total infections	35 (38.9)
Laboratory results	**N (% or average)**
Leukopenia [WBC <3700 μL]	1 (1.1%)
AST/ALT >2× normal	1 (1.1%)
TG average increase, mg/dL	6 (32)
Total cholesterol average increase, mg/dL	15 (50.2)
LDL average increase, mg/dL	15 (32.2)

Malignancy	N (%)
New	0 (0.0)
Recurrent	0 (0.0)
Other	**N (%)**
Headache	13 (14.4)
Acne	7 (7.8)
Fatigue	6 (6.7)
Weight gain	6 (6.7)
Night sweats	4 (4.4)
Folliculitis	3 (3.3)
Nausea	2 (2.2)
Diarrhea	1 (1.1)
Abdominal pain	1 (1.1)
Bruising	1 (1.1)
Palpitations	1 (1.1)
Numbness	1 (1.1)
Verruca vulgaris	1 (1.1)
Tinnitus	1 (1.1)

ALT, Alanine aminotransferase; *AST*, aspartate aminotransferase; *LDL*, low-density lipoprotein; *TG*, triglycerides; *URI*, upper respiratory infection; *UTI*, urinary tract infection; *WBC*, white blood cell count.

robust response to tofacitinib 5 mg twice daily. Although previous studies do not show a significant benefit of pulsed prednisone on AT or AU,[9,10] its use together with tofacitinib in this study was associated with sustained hair regrowth in patients who were not demonstrating significant regrowth with tofacitinib monotherapy. It may be that the addition of a brief course of intermittent, high-dose prednisone to tofacitinib accelerates hair regrowth.

Biologically and clinically important findings of this study relate to duration of hair loss, in particular the time since hair follicles last grew hair. First, after 10 years of complete scalp hair loss, patients are much less likely to respond to treatment with tofacitinib. Second, with each year leading up to 10 years of complete scalp hair loss, there is a trend toward decreased likelihood of complete hair regrowth. These findings suggest that intervention is important before disease duration in patients with AT or AU approaches 10 years or else chances of hair regrowth diminish.

Female patients experienced a higher median percent change in SALT score than male patients (66.5% vs 61.0%, P = .25), although this difference was not statistically significant. This may be in part attributable to concomitant androgenetic alopecia, which affects approximately 50% of the male population.[11] Indeed, hair regrowth in some male patients in our study revealed androgenetic alopecia, and therefore the percent change in SALT score for these patients may have been underestimated.

An analysis of efficacy must account for disease relapse (patchy or complete scalp hair loss), which occurred in 8 patients (12.3%) during treatment, 3 of whom were on tapered doses of tofacitinib after complete response and 5 of whom were on the same dose with which they had been experiencing hair regrowth before relapse. Subsequent to relapse, hair regrowth was again achieved in 5 patients with standard monotherapy and in 2 patients with adjuvant therapy; 1 patient decided not to continue therapy. These observations suggest that maintenance therapy may be necessary for continued remission of disease.

The safety profile of tofacitinib in this group of patients was favorable, and no serious adverse events were observed over a median duration of 12 months of treatment. Interestingly, acne vulgaris (new or worsening disease) occurred in nearly 8% of patients and, to our knowledge, this has not previously been reported with tofacitinib in other diseases. It is important to note that in clinical trials of tofacitinib for rheumatoid arthritis, solid organ malignancy, lymphoma, and serious infections requiring hospitalization were observed, although rheumatoid arthritis itself is associated with increased risk of malignancy.[12-14]

In summary, long-term use of tofacitinib was effective and well tolerated for the treatment of severe AA, AT, and AU. AA is a common disorder associated with a significant negative impact on health-related quality of life[15] as well as high rates of depression and anxiety,[16] which makes

recent therapeutic progress vitally important. The expanded experience regarding treatment of severe AA provided by this study will help to guide clinical trials, which will be important for detailing the efficacy and safety of JAK inhibitors in this disease.

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