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Characteristics and Outcomes of Patients on Tofacitinib for Alopecia Areata or Rheumatoid Arthritis: A Retrospective Cohort Study

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Abstract: Tofacitinib is a Janus kinase inhibitor (JAKi) that is used off-label for the treatment of alopecia areata (AA). Its boxed warning includes an increased risk of serious adverse events (SAEs) based on the results of a safety trial in rheumatoid arthritis (RA) patients taking the medication. The purpose of this study was to investigate the differences in patients' characteristics and SAEs profiles between RA and AA populations taking tofacitinib. The cohorts were constructed using the TrinetX database to identify the patients who were prescribed tofacitinib for RA or AA between October 2012 and October 2023. A total of 22,873 patients were included in this analysis, with 21,080 individuals in the RA cohort and 1793 individuals in the AA cohort. After matching for age, sex, and race, each cohort had a sample size of 1482. Data on the patients' sex, age, race, comorbidities, concomitant medications, and associated SAEs were collected. The cohorts were compared by calculating the odds ratios and tested for significance associations using Fisher's Exact Tests. Both the RA and AA cohorts were predominantly female (RA 79%, AA 70%), with mean ages of 61 $\pm$ 14 years and 38 $\pm$ 19 years (p-value < 0.0001), respectively. Both the groups showed similar racial distributions. The RA cohort had increased rates of hypertension, obesity, type 2 diabetes mellitus, and nicotine dependence compared to those of the AA cohort (p-value < 0.0001). With the exception of cyclosporine and azathioprine, the percentage of concomitant medication use was higher in all the categories in the RA cohort than those in the AA cohort (p-value < 0.0001). Higher rates of adverse events were seen in the RA cohort across all the categories, except myocardial infarction, stroke, and lymphomas/hematopoietic malignancies. Our findings show that the SAEs on the boxed warning of tofacitinib should be strongly considered when being used off-label for the treatment of AA. Clinicians must carefully assess the individual patient factors when determining the appropriateness of tofacitinib use.

Keywords: tofacitinib; JAK inhibitors; alopecia; alopecia areata; rheumatoid arthritis; adverse events; pulmonary embolism; myocardial infarction; infection; lymphoma

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1. Introduction

Janus kinase inhibitors (JAKis) are gaining popularity as a treatment for alopecia areata (AA), an immune-mediated condition characterized by non-scarring hair loss. This class of medications has particularly become a desirable option for AA patients with a severe or refractory disease [1,2] following the recent approval of JAKis baricitinib and ritlecitinib for AA and an increase in research supporting the efficacy of JAKi in treating AA [3,4]. Despite being viewed as a promising new alternative, these drugs are not without their shortcomings. Based on the data from a safety trial of rheumatoid arthritis (RA) patients taking tofacitnib [5], the FDA issued revisions to the boxed warnings for JAKis tofacitinib, upadacitinib, and baricitinib in 2021. These updates cautioned of an increased risk in serious adverse events (SAEs): infections, cardiovascular events, venous thromboembolism,

and malignancies. These safety concerns were further validated by real-world evidence of RA patients taking tofacitinib [6,7].

Tofacitinib is not approved for the treatment of AA, but successful hair regrowth with its off-label use has been reported in several studies [4,8–10]. While the risk of SAEs in patients taking tofacitinib for RA has been well studied, there is a lack of data comparing this population to a population of patients on tofacitinib for AA. The expectations of tofacitinib-associated SAEs drawn from RA patient data may not apply to the AA population. Therefore, comparative analysis discerning the differences in the characteristics and outcomes between the two groups is needed. This study investigates the differences in characteristics and outcomes between the AA and RA patients prescribed tofacitinib to give insights into population-specific SAEs.

2. Results

2.1. Patient Characteristics

A total of 22,873 patients were included in this analysis. The RA cohort consisted of 21,080 individuals, and the AA cohort consisted of 1793 individuals. Following propensity score matching for age, sex, and race, each cohort had a sample size of 1482. The mean age of the RA cohort was 61 ± 14 years and was predominantly female (79%). The mean age of the AA cohort was 38 ± 19 years (p-value < 0.0001), which was significantly lower than the RA cohort, and it also showed a female predominance 70% (p-value < 0.001). The racial proportions of White, Black or African American, Asian, and other/unknown race patients in the RA cohort were 71%, 10%, 3%, and 14%, respectively. In the AA cohort, the racial proportions of White, Black or African American, Asian, and other/unknown race patients were 68%,14%, 4%, and 18%, respectively (Table 1).

Table 1. Clinical characteristics of alopecia areata (AA) and rheumatoid arthritis (RA) patients on tofacitinib.

Characteristics	RA	AA	*p*-Value
	***n* = 21,080**	***n* = 1793**	
Demographics			
Age, mean (SD)	61 (14)	38 (19)	<0.0001
Sex, no (%)			
Female	16,590 (79)	1239 (70)	<0.0001
Male	3953 (19)	519 (29)	<0.0001
Race, no (%)			
White	14,900 (71)	1210 (68)	0.04
Black or African American	2211 (10)	167 (14)	0.16
Asian	720 (3)	70 (4)	0.23
Other/Unknown Race	2866 (14)	311 (18)	0.04
Comorbidities, no (%)			
Hypertension	8894 (39)	190 (11)	<0.0001
Obesity	4311 (20)	182 (10)	<0.0001
Type 2 diabetes mellitus	3035 (14)	77 (4)	<0.0001
Nicotine Dependence	2194 (10)	59 (3)	<0.0001
Concomitant Immunomodulating Medications, no (%)			
Methotrexate	11,169 (53)	372 (21)	<0.0001
Prednisone	13,619 (64)	661 (37)	<0.0001
Rituximab	1014 (5)	15 (1)	<0.0001
Hydroxychloroquine	7229 (34)	146 (8)	<0.0001
Cyclosporine	1025 (5)	92 (5)	0.56
Azathioprine	964 (5)	68 (4)	0.14
Mycophenolate mofetil	398 (2)	75 (4)	<0.0001

AA, alopecia areata; RA, rheumatoid arthritis; SD, Standard Deviation.

2.2. Comorbidities

The prevalence of comorbidities within the RA and AA cohorts demonstrated notable differences. In the RA cohort, 39% had hypertension, 20% were affected by obesity, 14% had type 2 diabetes mellitus, and 10% experienced nicotine dependence. In the AA cohort, the prevalences differed with 21% (p-value < 0.0001) affected by hypertension, 11% (p-value < 0.0001) by obesity, 10% (p-value < 0.0001) by type 2 diabetes mellitus, and 4% (p-value < 0.0001) by nicotine dependence (Table 1).

2.3. Concominant Medications

The percentage of concomitant medication use was higher across all categories in the RA patient cohort compared to that of the AA patient cohort, except for cyclosporine and azathioprine. The percentages of medication use in the RA cohort were as follows: 53% used methotrexate, 64% used prednisone, 5% used rituximab, 34% used hydroxychloroquine, 5% used cyclosporine, 5% used azathioprine, and 2% used mycophenolate mofetil. In the AA cohort, the percentages of medication use were as follows: 21% used methotrexate (p-value < 0.0001), 37% used prednisone (p-value < 0.0001), 1% used rituximab (p-value < 0.0001), 8% used hydroxychloroquine (p-value < 0.0001), 5% used cyclosporine (p-value = 0.56), 4% used azathioprine (p-value = 0.14), and 4% used mycophenolate mofetil (p-value < 0.0001) (Table 1).

2.4. Adverse Events

Adverse events were present at higher rates in the RA cohort in all the categories included within this study, with exception to myocardial infarction, stroke, and lymphomas/hematopoietic malignancies. Infections were more prevalent among the RA patients compared to those with AA, with urinary tract infections reported in 5% of the RA cases compared to 2% in those with AA (OR = 2.7, p-value < 0.0001). Rare opportunistic infections were observed in 8% of the RA cases, while this figure stood at 6% for those with AA (OR = 1.4, p-value = 0.02). Upper respiratory tract infections were reported in 8% of the RA patients and 6% of the AA cases (OR = 1.5, p-value = 0.01). Cardiovascular events, including myocardial infarction and stroke, were present at similar rates between the RA patients and AA patients. Myocardial infarction was reported in 1% of the RA patients and 0.7% of the AA patients (OR = 1.5, p-value = 0.31), while stroke was also reported in 1% of the RA patients and 0.7% of the AA patients (OR = 1.9, p-value = 0.09). Non-lymphoma/hematopoietic malignancies occurred in 5% of the RA cases and 7% of the AA cases (OR = 0.6, p-value = 0.002). Lymphomas and hematopoietic malignancies were reported in 0.7% of both the AA and RA cases (OR = 1.0, p-value = 0.997). Thromboembolic events were more common in the RA patients, at 3%, compared to 1% in the AA cases (OR = 2.3, p-value = 0.004) (Table 2).

Table 2. Serious adverse events in patients with alopecia areata (AA) and rheumatoid arthritis (RA) on tofacitinib (odds ratio) between age-, sex-, and race-matched cohorts.

Outcomes	RA, no (%) (n = 1492)	AA, no (%) (n = 1492)	Odds Ratio RA/AA, (95% CI)	p-Value
Infection				
Urinary Tract Infection	61 (5)	24 (2)	2.7 (1.7–4.3)	<0.0001
Upper Respiratory Tract Infections	96 (8)	71 (6)	1.5 (1.1–2.1)	0.01
Rare Opportunistic Infections	107 (8)	76 (6)	1.4 (1.1–2.0)	0.02
Thromboembolic events	39 (3)	18 (1)	2.3 (1.3–4.0)	0.004
Cardiovascular disease				
Stroke	19 (1)	10 (0.7)	1.9 (0.9–4.1)	0.09
Myocardial Infarction	15 (1)	10 (0.7)	1.5 (0.7–3.4)	0.31

Table 2. *Cont.*

Outcomes	RA, no (%) (*n* = 1492)	AA, no (%) (*n* = 1492)	Odds Ratio RA/AA, (95% CI)	*p*-Value
Lymphomas and Hematopoietic Malignancies	10 (0.7)	10 (0.7)	1.0 (0.4–2.4)	0.997
Non-Lymphoma/ Hematopoietic Malignancies	62 (5)	97 (7)	0.6 (0.4–0.8)	0.002

AA, alopecia areata; RA, rheumatoid arthritis; CI, Confidence Interval.

3. Discussion

This retrospective cohort study investigated the characteristics and SAEs of patients prescribed tofacitinib for either RA or AA. Although the SAEs of patients taking tofacitinib for RA have been well studied, it may be useful to also examine the characteristics and outcomes of the AA patients on tofacitinib given the increase in its off-label use for AA. RA is associated with a broader range of potential medical issues due to its systemic involvement, and the absence of comparative data between these populations may lead to inappropriate extrapolations of RA-based data as a predictor for AA outcomes. This is particularly relevant because tofacitinib is not approved for the treatment of AA. Conversely, some may use the tendency of AA as a condition that is not typically associated with systemic effects as reasoning to undermine the SAEs of tofacitinib's black box warning when the drug is used for AA treatment.

In our study, both the cohorts were predominantly female and White, but the AA cohort was younger in comparison to the RA one (a mean age of 38 years vs. 61 years). The RA cohort had a higher prevalence of comorbidities, including hypertension, type 2 diabetes mellitus, obesity, and nicotine dependence, which is likely reflective of their older age. The concomitant immunosuppressive medication use rate was also higher in the RA cohort compared to that of the AA cohort, with exception to cyclosporine and azathioprine. It is important to note that the increased utilization of other immunosuppressive medications and biologic agents by rheumatoid arthritis (RA) patients may have influenced their overall health outcomes (Table 1).

To minimize the confounding variables and to enhance the validity of our outcome analysis, the cohorts were matched by age, sex, and race. Both the cohorts had similar rates of myocardial infarction, stroke, and lymphomas/hematopoietic malignancies after matching. However, the RA cohort had significantly higher rates of infections, thromboembolic events, and non-lymphomas/hematopoietic malignancies (Table 2). Our results are consistent with the other studies investigating adverse events in patients taking tofacitinib for RA [5,11]. Notably, our findings show that in comparison to the RA patients, the AA patients have lower risks of infections, thromboembolic events, and non-lymphomas/hematopoietic malignancies. Nevertheless, the boxed warning for tofacitinib should be strongly considered when used off-label for the treatment of AA. Clinicians must carefully assess the individual patient factors when determining the appropriateness of off-label tofacitinib use. Larger clinical trials of tofacitinib use in AA patients are needed to further examine these risks.

Study Limitations

Despite the valuable insights obtained from TrinetX, several limitations need consideration. Data quality concerns arise due to the variations in accuracy, completeness, and consistency among healthcare providers contributing to the network. Our results only encompass the reported data; therefore, it is not fully representative of all the adverse events within the population. While TrinetX offers extensive real-world data, its generalizability may be constrained by the potential biases in data representation, limiting the applicability of findings to broader populations or different healthcare contexts. Although it would have been ideal to control-match the cohorts for other immunosuppressive agents

or concomitant diseases to conduct more robust statistical analysis, the software used in this study restricts the number of covariables that can be matched. This limitation may introduce some distortion in our results by overestimating the adverse outcomes in the RA cohort and attributing them to tofacitinib rather than other drugs or illnesses. Lastly, maintaining consistent quality control across diverse data sources within TrinetX poses challenges, potentially impacting the reliability of analyses. These limitations emphasize the need for cautious interpretation and acknowledgment of potential biases in research utilizing TrinetX data, especially given the relatively small sample sizes of each cohort in this study.

4. Materials and Methods

4.1. Data Source

TrinetX is a global database of patient data with built-in features of precise cohort building based on inclusion and exclusion criteria, propensity-score-matched cohorts based on selected covariates, and statistical tests and functions. The patient data in this manuscript were obtained from the "Global Collaborative Network" within TrinetX. Access to TrinetX was granted to the research team through the University of California Irvine School of Medicine.

4.2. Data Preparation and Cohort Selection

Both the RA and AA cohorts were constructed using the TrinetX database by identifying the patients with RA and AA who were prescribed tofacitinib between October 2012 and October 2023, excluding those with diagnosis overlap. Patient cohorts matched by age, race, and sex were also generated. Data on patients' sex, age, race, comorbidities, concomitant medications, and associated SAEs were collected. The ICD-10 codes used for comorbidities in both cohorts are as follows: Hypertensive Disease = I10–I16; obesity = E65–E68; type 2 diabetes mellitus = E11; and nicotine dependence = Z87.891. The RxNorm codes used for medications in both cohorts are as follows: methotrexate = 6851; prednisone = 8640; rituximab = 121,191; hydroxychloroquine = 5521; cyclosporine = 3008; azathioprine = 1256; and mycophenolate mofetil = 68,149. The ICD-10 codes used to analyze adverse outcomes are as follows: upper respiratory tract infection = J00–J06; rare opportunistic infections = A15–A19, B00, B25, B37, B39, B45, B59, and CVX188 (Tuberculosis, Herpesviral, Cytomegaloviral disease, Candidiasis, Histoplasmosis, Cryptococcosis, Pneumocystosis, and Zoster, respectively); urinary tract infection = N39.0; myocardial infarction = I21; stroke = I63, non-lymphoma/hematopoietic malignancies = C00–C26, C30–C80, C7A, and D37–D49; lymphomas/hematopoietic malignancies = C81–C96; and thromboembolic events = I26,I82.

4.3. Statistical Analysis

The patients' characteristics and outcome variables were compared by calculating odds ratios and subsequently confirmed with Fisher's Exact Tests to test for significance associations. Categorical values are presented as number (n) and frequencies (%). Table 1 presents the unmatched data, while Table 2 presents the propensity score matching for the variables of age, sex, and race. Results with p-values < 0.05 were considered statistically significant.

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References

1. Esteves, M.; Lopes, S.; Azevedo, F.; Pedrosa, A. Effectiveness of Oral Tofacitinib Dose Tapering in a Case of Alopecia Areata Universalis. *Ski. Appendage Disord.* **2021**, *7*, 36–40. [CrossRef] [PubMed]
2. Cheng, M.W.; Kehl, A.; Worswick, S.; Goh, C. Successful Treatment of Severe Alopecia Areata With Oral or Topical Tofacitinib. *J. Drugs Dermatol.* **2018**, *17*, 800–803. [PubMed]
3. Liu, M.; Gao, Y.; Yuan, Y.; Yang, K.; Shen, C.; Wang, J.; Tian, J. Janus Kinase Inhibitors for Alopecia Areata. *JAMA Netw. Open* **2023**, *6*, e2320351. [CrossRef]
4. Yan, D.; Fan, H.; Chen, M.; Xia, L.; Wang, S.; Dong, W.; Wang, Q.; Niu, S.; Rao, H.; Chen, L.; et al. The efficacy and safety of JAK inhibitors for alopecia areata: A systematic review and meta-analysis of prospective studies. *Front. Pharmacol.* **2022**, *13*, 950450. [CrossRef]
5. Ytterberg, S.R.; Bhatt, D.L.; Mikuls, T.R.; Koch, G.G.; Fleischmann, R.; Rivas, J.L.; Germino, R.; Menon, S.; Sun, Y.; Wang, C.; et al. Cardiovascular and Cancer Risk with Tofacitinib in Rheumatoid Arthritis. *N. Engl. J. Med.* **2022**, *386*, 316–326. [CrossRef] [PubMed]
6. Convertino, I.; Lorenzoni, V.; Gini, R.; Turchetti, G.; Fini, E.; Giometto, S.; Bartolini, C.; Paoletti, O.; Ferraro, S.; Cappello, E.; et al. Drug-Utilization, Healthcare Facilities Accesses and Costs of the First Generation of JAK Inhibitors in Rheumatoid Arthritis. *Pharmaceuticals* **2023**, *16*, 465. [CrossRef] [PubMed]
7. Bertoldi, I.; Caporali, R. Tofacitinib: Real-World Data and Treatment Persistence in Rheumatoid Arthritis. *Open Access Rheumatol. Res. Rev.* **2021**, *13*, 221–237. [CrossRef] [PubMed]
8. Tegtmeyer, K.; Zhao, J.; Maloney, N.J.; Atassi, G.; Beestrum, M.; Lio, P.A. Off-label studies on tofacitinib in dermatology: A review. *J. Dermatol. Treat.* **2021**, *32*, 399–409. [CrossRef] [PubMed]
9. Ibrahim, O.; Bayart, C.B.; Hogan, S.; Piliang, M.; Bergfeld, W.F. Treatment of Alopecia Areata With Tofacitinib. *JAMA Dermatol.* **2017**, *153*, 600–602. [CrossRef] [PubMed]
10. Kołcz, K.; Żychowska, M.; Sawińska, E.; Reich, A. Alopecia Universalis in an Adolescent Successfully Treated with Upadacitinib—A Case Report and Review of the Literature on the Use of JAK Inhibitors in Pediatric Alopecia Areata. *Dermatol. Ther.* **2023**, *13*, 843–856. [CrossRef] [PubMed]
11. Papierzewska, M.; Waśkiel-Burnat, A.; Rudnicka, L. Safety of Janus Kinase inhibitors in Patients with Alopecia Areata: A Systematic Review. *Clin. Drug Investig.* **2023**, *43*, 325–334. [CrossRef] [PubMed]