Family history of psoriasis, psychological stressors, and tobacco use are associated with the development of tumor necrosis factor-α inhibitor-induced psoriasis: A case-control study

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Background: Tumor necrosis factor-α inhibitor—induced psoriasis (TNFI psoriasis) is a paradoxical reaction characterized by development of a psoriasiform rash that mimics psoriasis vulgaris. Temporal onset variability and low incidence rates suggest that underlying risk factors or outside triggers have a role in TNFI psoriasis initiation.

Objectives: We aimed to identify underlying risk factors and outside triggers associated with TNFI psoriasis onset.

Methods: This case-control study included 97 patients at a tertiary care center between 2003 and 2013 who developed TNFI psoriasis. Ninety-seven control patients were matched to age, sex, disease, TNF-α inhibitor, and length of time on treatment before TNFI psoriasis onset. Patient medical records were reviewed ≥6 months immediately preceding TNFI psoriasis onset (similar equivalent time point for matched controls) for information about potential risk factors and outside factors categorized as: (1) serologic abnormalities, (2) acute events, and (3) social factors.

Results: Compared with those of matched controls, odds ratios (ORs) were significantly higher in the TNFI psoriasis group for psoriasis family history (OR, 16.0) and acute psychological stressors (OR, 3.14) and marginally associated with tobacco use (OR, 1.76).

Conclusions: Our results suggest that psoriasis family history, psychological stressors, and tobacco use might be risk factors for developing TNFI psoriasis. Performing detailed patient histories when considering TNFI therapy may be useful in identifying patients at risk for TNFI-psoriasis. (J Am Acad Dermatol 2020;83:1599-605.)

Key words: family history; paradoxical psoriasis; psychological stress; risk factors; smoking; TNF-α inhibitor; TNF-α inhibitor-induced psoriasis; tobacco.

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Tumor necrosis factor-α inhibitors (TNFIs) have revolutionized our ability to treat chronic inflammatory diseases effectively, including psoriasis, rheumatoid arthritis, and inflammatory bowel disease (IBD). Like other immunosuppressive medications, TNFIs are associated with numerous adverse effects. One unique adverse effect is "paradoxical" development of a psoriasiform rash that mimics psoriasis vulgaris both clinically and histologically—referred to as *TNFI psoriasis*.[1] TNFI psoriasis can be severe enough to require discontinuation of the inciting TNFI despite effective control of the underlying indicated disease, underscoring the importance of better understanding this reaction.[2]

Despite well over 500 reported cases and knowledge of TNFI psoriasis for >15 years, our understanding of its pathogenesis is incomplete.[3-6] Interestingly, TNFI-psoriasis onset can occur at any time during TNFI treatment, from within 1 week of initiating treatment to several years after initiation.[4] Thus, it differs from most adverse drug reactions. In addition, only a small subset of patients exposed to TNFIs develop TNFI psoriasis, with incidence rates estimated at 1-3 per 1000 person-years.[7,8] This wide variability in temporal onset and low incidence rate raises the possibility that underlying risk factors or outside triggers, or both, are required for TNFI psoriasis initiation. We sought to explore the possibility that underlying risk factors and outside triggers contribute to the onset of TNFI psoriasis.

CAPSULE SUMMARY

- TNFI psoriasis is a paradoxical reaction associated with TNFI exposure. Risk factors for TNFI psoriasis are not well defined.
- In this study of 97 patients with TNFI psoriasis and matched controls, psoriasis family history (odds ratio, 16.0), acute psychological stressors (odds ratio, 3.14), and tobacco use (marginal; odds ratio, 1.76) are associated with and identified as potential risk factors for this reaction.

METHODS

Cleveland Clinic's electronic medical records (EMRs) were searched for patients who, during 2003-2013, had been exposed to a TNFI, had seen a dermatologist after a TNFI was first prescribed, and had been diagnosed with psoriasis, psoriasiform dermatitis, dermatitis, drug rash, or palmoplantar pustulosis after TNFI exposure. Detailed methods concerning how we identified patients with TNFI psoriasis are published elsewhere.[9] One hundred and two patients met our inclusion criteria for diagnosis of TNFI psoriasis, and their clinical characteristics and outcomes have been described.[9] Three additional patients with TNFI-induced psoriasis were identified prospectively by one author (A.P.F.) subsequent to publishing the previous cohort, thus increasing the total to 105 patients.

Control patients were identified in a similar EMR search of 2003-2015, except that these patients did not develop TNFI psoriasis in an equivalent time period of TNFI use or later. The use of an expanded time frame to 2015 was done to optimize chances of finding appropriately matched controls for our TNFI cohort. Eligible control patients were matched to sex, specific TNFI, age at TNFI initiation, underlying disease for which TNFIs were indicated, and equivalent months of follow-up after TNFI initiation.

For each patient, we reviewed EMR details starting 6 months immediately preceding TNFI psoriasis onset (6 months preceding equivalent time point for controls) to obtain information about potential triggers. Potential triggers were separated into 3 primary categories: (1) serologic abnormalities, (2) acute events, and (3) social factors. For social factors, we searched the patients' entire EMRs (beyond 6 months preceding TNFI psoriasis onset) for long-term habits (tobacco, alcohol, illicit drugs) or historical facts (family history of psoriasis) that are unlikely to change over time. Aligning with these thoughts, there were no documented changes within 6 months of TNFI psoriasis onset for the social factors we included in any patient's EMR. Family history of psoriasis was considered positive if it was specified that first-degree relatives had a history of psoriasis. Infectious diagnosis (skin infection, upper respiratory infection [URI], gastroenteritis) was accepted if documentation in clinic notes supported clinician confidence of the infection. Additional results (biopsies, cultures, imaging) were typically present but not required. Skin or soft tissue infection was defined as documented evidence of skin infection, furuncles, abscesses, or cellulitis. URI was defined as documented evidence of URI in clinic notes or the presence of cough or sore throat; gastroenteritis was defined as documented gastroenteritis or the presence of emesis or diarrhea.

Descriptive statistics such as count (%) and median (Q_1-Q_3) were used to summarize demographic and clinical data. Categorical data for each potential risk factor and outside trigger were analyzed using the McNemar test for matched case-control pairs. For each potential risk factor and outside trigger, the

Abbreviations used:

ANA: antinuclear antibody
CI: confidence interval
EMR: electronic medical record
IBD: inflammatory bowel disease
OR: odds ratio
TNFI: tumor necrosis factor-α inhibitor
URI: upper respiratory infection

strength of the association between the risk factor or trigger and TNFI-psoriasis was expressed using odds ratios (ORs) and 95% confidence intervals (CIs).

First, this study was performed as a complete-case analysis using only case-control pairs with a recorded history of the presence or absence of the potential risk factor or outside trigger for both pair members. In addition, to address the missing data issue, multiple imputation using chained equations was performed with $M = 10$ imputation sets. With this method, the distribution of the observed data is used to estimate multiple values of the missing data, which reflects the uncertainty around the true value. As missingness affected the risk factor and outside triggers differently, because of varying levels of recording in the EMR, we also reported the fraction of missing information, which is a measure of the uncertainty about the values being imputed for the missing elements. A significance level of 5% was used. Data analysis was performed using SAS version 9.4 (SAS Institute, Cary, NC).

RESULTS

Ninety-seven adequately matched case-control pairs were identified from our cohort of 105 patients with TNFI psoriasis (Table I). Approximately 73% of patients (71/97) were women, and average age at initiation of the inciting TNFI was approximately 41 years. Patients in our cohort developed TNFI psoriasis while exposed to 3 different TNFIs, with almost half being associated with infliximab. Average time to TNFI psoriasis onset was 9 months after TNFI initiation. As seen in Table I, time to nonreaction of TNFI psoriasis was slightly longer (10 months) in the control group because of the timing of when this population had documented clinical encounter notes compared with the TNFI psoriasis group. Twenty-one patients with TNFI psoriasis (21/97; 22.7%) had a personal history of psoriasis, only four of whom (4/21; 19.0%) had a positive family history of psoriasis.

Numerous potential triggers were evaluated within each predetermined category (serologic abnormalities, acute events, social factors; Table II). The percentage of missing data in patients' EMRs ranged from 3% (tobacco use) to 78% (antinuclear antibodies [ANAs]). Complete-case analysis and multiple imputation analysis each identified significant associations among risk factors and triggers and TNFI psoriasis (Table III). The complete-case analysis identified family history of psoriasis (24% vs 3%; $P = .0003$) and acute psychological stressors (96% vs 54%; $P = .0009$) as being associated with TNFI psoriasis development. In addition, tobacco use was found to be marginally associated with TNFI psoriasis (33% vs 22%; $P = .10$).

Table I. Demographic and clinical characteristics of TNFI-induced psoriasis cases and matched controls

Characteristics	TNFI psoriasis cases (N = 97)	Controls (N = 97)
Female sex	71 (73%)	71 (73%)
Age at start of medication, median years (range)	41 (21-52)	41 (21-52)
Time to TNFI-induced psoriasis or nonreaction, months (range)	9 (3-25)	10 (4-26)
TNF-α inhibitor		
Adalimumab	32 (33%)	32 (33%)
Etanercept	17 (18%)	17 (18%)
Infliximab	48 (50%)	48 (50%)

Descriptive statistics are reported as either count (%) or median (Q_1-Q_3).
TNF, Tumor necrosis factor; *TNFI*, tumor necrosis factor-α inhibitor.

The results are based on only a subset of the cohort because of missing data; therefore, it is important to consider how the results fluctuate under imputation methods. Therefore, we conducted a multiple imputation analysis (Table III). Multiple imputation analysis provided results similar to the complete-case analysis, identifying family history of psoriasis (OR, 5.54) and acute psychological stressors (OR, 3.14) as being significantly associated with TNFI psoriasis development, whereas tobacco use was found to be marginally associated with TNFI psoriasis (OR, 1.76). To quantify the uncertainty about the values imputed for the missing data points, the fraction of missing information is provided. It is important to note that ANA data, skin and soft tissue data, and URI data in our sample have high fractions of missing information; therefore; these results are only suggestive, and they must be interpreted with caution.

DISCUSSION

TNFI psoriasis was first described more than 15 years ago, and it is now a well-accepted but incompletely understood adverse reaction occurring in patients treated with TNFIs. The leading

Table II. Recorded data details of explored TNFI-induced psoriasis risk factors

Potential risk factor	Patients with TNFI psoriasis	Matched control patients
Social factors		
Family history of psoriasis		
Positive	17	2
Negative	70	77
Not recorded	10	18
Totals	97	97
History of tobacco use		
Positive	30	20
Negative	63	75
Not recorded	4	2
Totals	97	97
History of alcohol use		
Positive	45	52
Negative	41	37
Not recorded	11	8
Totals	97	97
History of illicit drug use		
Positive	5	3
Negative	73	76
Not recorded	19	18
Totals	97	97
Serologic abnormality history		
ANA within 6 mo of onset		
Positive	5	6
Negative	6	25
Not recorded	86	66
Totals	97	97
Elevated WBC count within 6 mo of onset		
Positive	12	15
Negative	58	65
Not recorded	27	17
Totals	97	97
Peripheral eosinophilia		
Positive	13	10
Negative	52	67
Not recorded	32	20
Totals	97	97
Acute event history		
Skin or soft tissue infection		
Positive	4	7
Negative	18	25
Not recorded	75	65
Totals	97	97
Upper respiratory infection		
Positive	15	31
Negative	1	1
Not recorded	81	65
Totals	97	97
Acute psychologic stressor within 6 mo of onset		
Positive	36	32
Negative	2	36
Not recorded	59	29
Totals	97	97
Gastroenteritis		
Positive	25	27
Negative	34	19
Not recorded	38	51
Totals	97	97

ANA, Antinuclear antibody; *WBC*, white blood cell.

hypothesis concerning TNFI psoriasis pathogenesis suggests that TNF-α blockade disrupts cytokine balance and can trigger this reaction. More specifically, it is hypothesized that TNF-α blockade allows plasmacytoid dendritic cells to produce interferon-α unopposed and without adequate regulation.[10] Although there is recent evidence to support this hypothesis, it does not necessarily account for why only a small subset of patients develop TNFI psoriasis or why temporal onset can vary from individual to individual.[11]

Here we report a case-control study comparing 97 patients with TNFI psoriasis with matched controls. In this study, family history of psoriasis was the strongest potential risk factor for development of TNFI psoriasis. Although to our knowledge a case-control study examining associations and potential risk factors of TNFI psoriasis has not been reported previously, many reported TNFI psoriasis cohorts have found at least some patients with a positive family history of psoriasis. In one study, family history of psoriasis was found to be a marginally significant risk factor for TNFI-psoriasis development.[12] In the Mayo Clinic's cohort, 23% of patients (13/56) had a positive family history of psoriasis.[5] In several other cohorts, between 10% and 32% of patients had a positive family history of psoriasis.[13-16] In our study, 17.5% (17/97) of patients had a positive family history of psoriasis, consistent with prior TNFI psoriasis cohorts. Although we cannot completely exclude recall bias in patients who developed TNFI psoriasis, our study differed from previously reported cohorts in that we included a matched-control cohort, and all of our patients were examined and given diagnoses by dermatologists.

The suggestion that family history of psoriasis is a significant TNFI psoriasis potential risk factor implies that genetic factors are contributory. Indeed, genetic predisposition has been shown to be associated with TNFI psoriasis on several levels. In one study, patients with IBD who developed TNFI psoriasis had greater genetic predisposition toward psoriasis

Table III. Statistical comparison of patients with TNFI-induced psoriasis and matched controls

Risk factor or potential trigger	Complete case*					Multiple imputation†	Fraction missing information
	No. of pairs	TNFI psoriasis cases	Controls	McNemar *P* value	Odds ratio (95% CI)	Odds ratio (95% CI)	
Social factors							
Tobacco	91	30 (33%)	20 (22%)	.10	1.76 (0.86-3.80)	1.82 (0.93-3.54)	3%
Alcohol	81	45 (56%)	48 (59%)	.59	0.82 (0.38-1.78)	0.80 (0.40-1.58)	13%
Illicit drugs	65	5 (8%)	3 (5%)	.48	1.67 (0.32-10.73)	1.84 (0.42-8.00)	21%
Family history psoriasis	71	17 (24%)	2 (3%)	.0003	16.0 (2.5-671.0)	5.54 (1.48-20.73)	23%
Serologic abnormalities							
Positive ANA	7	2 (29%)	3 (43%)	.65	0.67 (0.06-5.82)	1.51 (0.79-2.89)	42%
Elevated WBC	57	10 (18%)	12 (21%)	.62	0.78 (0.25-2.35)	0.94 (0.42-2.12)	13%
Peripheral eosinophilia	49	8 (16%)	7 (14%)	.76	1.20 (0.31-4.97)	1.46 (0.56-3.83)	29%
Acute events							
Skin or soft tissue infection	7	2 (29%)	0 (0%)	.16	2.41 (0.29-∞)‡	0.93 (0.46-1.87)	44%
Upper respiratory infection	6	5 (83%)	6 (100%)	.32	1.00 (0.00-19.00)‡	0.60 (0.10-3.68)	43%
Acute psychological stressor	26	25 (96%)	14 (54%)	.0009	15.4 (3.2-∞)‡	3.14 (1.10-8.93)	53%
Gastroenteritis	29	11 (38%)	17 (59%)	.13	0.46 (0.12-1.42)	0.70 (0.38-1.30)	13%

Values are reported as a count (%) of patients with a reported history of the potential trigger before reaction or nonreaction (in controls).
ANA, Antinuclear antibody; *TNFI*, tumor necrosis factor-α inhibitor; *WBC*, white blood cell.
*The complete-case analysis included only case-control pairs for which a history of the risk factor and potential trigger being present or not present was available for both the cases and the controls.
†Multiple imputation based on $M = 10$ MICE imputations.
‡Indicates a median unbiased estimate and a one-sided confidence interval.

than control TNFI users who did not develop TNFI psoriasis.[17] In addition, genetic predisposition in these patients was similar to those with idiopathic psoriasis. In another study, 5 single-nucleotide polymorphisms were found to be significantly associated with TNFI psoriasis development, 3 of which were already known to be associated with psoriasis.[18]

Our study also identified acute psychological stressors as a significant potential TNFI psoriasis risk factor. Although this finding must be interpreted with caution because of the high fraction of missing information (53%), this potential risk factor would correlate with the wide temporal variability in TNFI psoriasis onset from patient to patient. Psychiatric reactions to life stressors are common and are known to be associated with immune dysfunction.[19] In a Swedish cohort study that included more than 100,000 patients with new-onset stress-related disorders, incidence of autoimmune disorders (mean 10-year follow-up) was found to be significantly higher than in a matched control population without stress-related disorders.[19] This result included a significant increased psoriasis incidence in the cohort with new-onset stress-related disorders (OR, 1.34; 95% CI, 1.26-1.42). It is hypothesized that psychological stress can activate the autonomic nervous system and disinhibit inflammatory responses.[20] In addition, the association of psychologic stress with lower cortisol levels could amplify production of proinflammatory cytokines.[20] Along these lines, patients with psoriasis persistently experiencing high levels of daily stressors had significantly lower basal cortisol levels compared with patients with persistent low levels of daily stressors in one study.[21] Furthermore, stress in patients with psoriasis has been correlated with flaring of disease shortly after peak stress levels.[22] Thus, previous work suggests that psychological stress could induce an inflammatory response conducive to development of TNFI psoriasis. To our knowledge, no previous study has explored the association of psychological stress with TNFI psoriasis, making this a novel finding in our study.

Smoking is a known risk factor for development of psoriasis vulgaris.[23] We found that smoking might also be a potential risk factor for TNFI psoriasis, being associated with marginal significance in our sample (OR, 1.76; 95% CI, 0.86-3.80). This marginal significance persisted with imputation analysis (OR, 1.82; 95% CI, 0.93-3.54). Several previous studies have also concluded that smoking is a risk factor for TNFI psoriasis, mostly in patients with IBD. In one study of 434 patients with IBD treated with TNFIs, smoking was found to be the strongest risk factor for the development of TNFI psoriasis (OR, 4.24; 95% CI, 1.55-13.60).[8] An additional study of 402 patients with IBD treated with TNFIs also found that smoking was an independent risk factor for the development of TNFI psoriasis (hazard ratio, 2.37; 95% CI, 1.36-4.48).[12] Finally, in a large cohort of 7415 patients with IBD, only smoking or formerly smoking (hazard

ratio, 2.1; 95% CI, 1.4-33.0) and female sex were significant risk factors for developing TNFI psoriasis.[13] Although many of our patients did have IBD, we included patients with other primary diseases in our cohort, which more closely resembles the occurrence of TNFI psoriasis in real-life practice. In addition, we compared our patients with TNFI psoriasis to matched controls.

Our analysis did not identify any other significant associations with TNFI psoriasis, including alcohol use, peripheral eosinophilia, or specific infections. The relationship between alcohol use and psoriasis is complex. Although some studies have suggested that alcohol use is a risk factor for typical psoriasis development, a recent systematic review concluded that there is insufficient evidence for this conclusion.[24] On the other hand, some studies suggest that chronic alcohol use likely results in dendritic cell abnormalities that result in cutaneous immune deficiency and decreased psoriasis risk.[8,25-28] For some of the factors we explored, including ANA, skin and soft tissue infections, and URIs, data were too sparse and had fractions of missing information that were too high to be conclusive.

Although this study identified potential TNFI psoriasis risk factors, it failed to identify potential triggers for the reaction other than acute psychological stressors that might help to explain the wide temporal variability in TNFI psoriasis onset from patient to patient. A possible reason for this result is that the retrospective nature of our study is associated with known limitations, and recent events such as infections or surgeries might not have been adequately documented in some notes. On the other hand, even prospective studies exploring such triggers are limited to some degree by patient recall bias concerning events leading up to onset of TNFI psoriasis. Together, these factors contributed to missing data in our complete-case analysis, which ranged from 3% to 78%. However, such associations and potential risk factors are known to be extremely challenging to identify. For example, although onset of typical psoriasis vulgaris is thought to require outside triggers, few have been identified objectively.

Our study had other limitations. Although this cohort included mostly patients without a history of psoriasis, a subset did have a history of psoriasis (19%). This finding is characteristic of previously reported TNFI psoriasis cohorts.[1,5,16,29-31] In many TNFI psoriasis cohorts, patients commonly develop psoriasis subtypes while taking TNFIs that differed from their previous psoriasis lesions.[16,32] Our inclusion criteria required that patients exhibited this characteristic (new psoriasis subtypes) to optimize chances such patients actually had TNFI psoriasis as opposed to recurrence of previous psoriasis. In addition, we cannot rule out an association between certain underlying diseases and TNFI psoriasis, because we matched patients with TNFI psoriasis on the basis of an underlying disease indication prompting TNFI initiation. Although no evidence of such an association exists and reported TNFI psoriasis cohorts vary in terms of most common underlying diagnoses, it is possible that reporting bias has led to an important association being currently undiscovered. Furthermore, it is possible that our definition of URI resulted in inclusion of patients with alternative disorders that affected analyses. Finally, while we found that psoriasis family history, acute psychological stressors, and tobacco use are associated with the development of TNFI psoriasis in our cohort, it is important to state that this is not evidence of a causal relationship.

CONCLUSION

This case-control study suggests that family history of psoriasis, acute psychological stressors, and tobacco use are risk factors for the development of TNFI psoriasis. Performing a detailed family history and social history during patient encounters when considering TNFI therapy can be useful in identifying patients to counsel about risk of this reaction. In current smokers, it would be reasonable to emphasize that smoking cessation could potentially decrease TNFI psoriasis risk, in addition to its many other obvious health benefits. Additional studies are needed to confirm our associations and to explore for external triggers that might contribute to TNFI-psoriasis development.

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