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TNF-alpha inhibitor-induced psoriasis: systematic review of clinical features, histopathological findings, and management experience

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CAPSULE SUMMARY

What is already known on this topic

- The paradoxical development of psoriasis is an unintended consequence of TNFα inhibition.

What this article adds to our knowledge

- Discontinuing TNFα therapy resulted in psoriasis resolution (47.7%) more often than in those who switched (36.7%) or continued (32.9%) TNFα therapy

How this information impacts clinical practice and/or changes patient care

- TNFα inhibitor-induced psoriasis is often successfully managed with skin-directed therapies and in many cases does not require cessation of TNFα inhibitor treatment.

INTRODUCTION

The proinflammatory cytokine tumor necrosis factor-alpha (TNFα) has been implicated in the pathogenesis of multiple inflammatory and autoimmune conditions such as Crohn's disease (CD), ulcerative colitis (UC), rheumatoid arthritis (RA), ankylosing spondylitis (AS), and psoriasis. The development of TNFα inhibitors has dramatically improved therapeutic options for patients with these conditions. However, there are many reports in the literature of TNFα inhibitors paradoxically inducing new onset psoriasis or worsening pre-existing quiescent psoriatic disease. A study analyzing the United States Food and

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Drug Administration Adverse Event Reporting System from 2004–2011 found that TNFα inhibitors used in the treatment of Crohn's Disease were associated with an increased risk of psoriasiform adverse events compared to other medications.[1] There is currently no standardized approach for managing TNFα inhibitor-induced psoriasis, and there is little clarity on whether to withdraw TNFα inhibitor therapy.

The objective of this systematic review of reported cases of TNFα inhibitor-induced psoriasis was to better define the demographic, clinical, and histological features of TNFα inhibitor-induced psoriasis and determine the optimal treatment approach.

METHODS

We conducted an electronic literature search to identify studies, case reports, and case series that documented new-onset psoriasiform lesions in patients being treated with a TNFα inhibitor (Fig. 1).

Information Sources and Search Strategy

With the assistance of a research librarian, we identified literature on PubMed on June 18, 2013 using the terms "anti-TNF-alpha", "TNF-alpha inhibitor", "TNF-alpha inhibitors", "TNF-alpha antagonist", "TNF-alpha antagonists", "anti-tumor necrosis factor", "tumor necrosis factor inhibitor", "tumor necrosis factor inhibitors", "tumor necrosis factor antagonist", "tumor necrosis factor antagonists", "infliximab", "adalimumab", "etanercept", "golimumab", "certolizumab", "psoriasis", "psoriasiform"[MeSH], "palmoplantar"[MeSH], "pustul*", "induce*", "cause*", "complicat*", "due", "flar*", "exacerbat*", "paradox*", "induct*", "induce*", "advers*", "onset", "associat*", "risk", "nonpsoriatic", "psoriasis/chemically induced"[MeSH], "Tumor Necrosis Factor-alpha/adverse effects"[MeSH]. We restricted the search results to English only records. We conducted similar computerized searches using SCOPUS and the Cochrane Database. The last search was conducted on July 1, 2014. Additionally, we reviewed citations within the identified articles and relevant reviews to locate published articles missed by database searches. We performed an EndNote function to identify and remove duplicates.

Study Selection

Two investigators (MH and MW) assessed study eligibility using title and abstract for initial screening. Two additional investigators (EW and GB) further evaluated the eligibility of the studies by reviewing the full-text publication. Any study that reported individual data of patients with new-onset psoriasis after the initiation of a TNFα inhibitor was eligible for inclusion. We excluded records that omitted specific data regarding individual patients, as well as cases in which the patient had a prior history of psoriasis.

Data Collection and Extraction

Two reviewers (EW and GB) independently extracted individual patient data from each record. We constructed a data collection spreadsheet and extracted the following data items from each record: patient demographics (including age, gender, ethnicity), age at onset of psoriasiform eruption, family history of psoriasis, prior TNFα inhibitor medication history,

disease being treated, TNFα inhibitor resulting in psoriasiform eruption, time elapsed prior to onset of psoriasiform eruption, morphology of psoriasiform lesions, body areas involved, biopsy result, recurrence with TNFα inhibitor switch, concomitant immunomodulator, concomitant systemic steroids, management and response.

RESULTS

Clinical and Histopathologic Characteristics

Of the 190 full-text articles assessed for eligibility, 88 articles met inclusion criteria for the final analysis. We extracted a total of 216 cases of new-onset TNFα inhibitor-induced psoriasis from these publications. Demographic features of patients with TNFα inhibitor-induced psoriasis are summarized in Table 1.

Women comprised 72.2% of the cases, with a female predominance in RA and CD (89.9% and 63.2%, respectively). Ages of psoriasis onset ranged from 7 years to 83 years; the mean age of psoriasis onset was 38.5 years. The majority of patients received TNFα inhibitor therapy for CD (40.7%), RA (37.0%), or AS (13.9%). Patients had a positive family history of psoriasis in 11.8% (N=19) of disclosed cases (N=161), and no patients had a personal history of psoriasis or psoriatic arthritis, as those cases were excluded. There were no identified cases with known pre-existing psoriatic arthritis prior to developing psoriasis on TNFα inhibitor therapy.

The psoriasis presentations were variable, and 26.9% of patients had more than one reported morphological type. The two most commonly observed clinical presentations included plaque (44.8%) and palmoplantar pustular (36.3%) psoriasis. Other presentations included ill-defined psoriasiform dermatitis (19.9%), severe scalp involvement associated with alopecia (7.5%), and generalized pustular psoriasis (10.9%). The anatomical sites commonly involved included soles (45.8%), extremities (45.4%), palms (44.9%), scalp (36.1%), and trunk (32.4%).

Of the 102 cases confirmed with biopsy, 54.9% revealed plaque psoriasis and 33.3% were consistent with pustular psoriasis with the remainder interpreted as psoriasiform dermatitis. An eosinophil rich infiltrate was noted in 3 of the plaque psoriasis biopsies and 3 of the pustular psoriasis biopsies.

TNFα Inhibitor Treatment Characteristics

The majority of cases were associated with infliximab (62.5%), followed by adalimumab (21.8%) and etanercept (14.4%). Only 2 cases involved certolizumab and 1 case with golimumab. The most commonly prescribed agent was infliximab (62.5%), with the majority of patients with CD and AS receiving infliximab compared to other agents (CD 82.8%; AS 73.3%). Patients underwent TNFα inhibitor therapy for an average of 14.0 months prior to onset (infliximab 13.6; adalimumab 14.4; etanercept 16.2, certolizumab 5.0, golimumab 4.0; overall range 1 to 120 months). Although 69.9% of patients experienced the onset of psoriasis in the first year of treatment, 31.2% of cases occurred in the second year (infliximab 17.4%; adalimumab 9.8%; etanercept 13.3%). 19 patients reported prior TNFα inhibitor treatment, 3 of which had previously experienced psoriasiform eruption and

resolution with withdrawal. The most common concomitant immunomodulators at the time of psoriasis onset included methotrexate (MTX; 33.7%), azathioprine (AZA; 18.9%), and leflunomide (13.7%). 17 cases reported administration of concomitant systemic steroids.

Management and Outcomes

Therapeutic management and outcomes of TNFα inhibitor-induced psoriasis are summarized in Table 2. Resolution of psoriasis (or no evidence of recurrence at time of follow-up) was reported in patients who discontinued TNF therapy (47.7%), switched to a different TNF agent (36.7%), or continued the same TNF therapy (32.9%). Improvement but incomplete resolution of psoriasis was reported in patients who continued the same TNF therapy (57.3%), discontinued TNF therapy (46.2%), and switched to a different TNF agent (18.4%). Regardless of the TNFα inhibitor treatment decision, the majority of patients received skin-directed therapy with one or more agents including topical steroids (76.5%), vitamin D analogues (17.6%), MTX (17.2%), phototherapy (8.3%), cyclosporine (5.4%), acitretin (2.0%), and coal tar (1.0%).

Management strategies and resulting outcomes were analyzed for patients with more severe presentations, including alopecia and/or generalized pustular psoriasis (Table 3). Half of the patients with alopecia had resolution of symptoms regardless of continuing or discontinuing TNF therapy (resolution in 2/4 who continued vs. 4/8 who discontinued therapy). Patients with generalized pustular psoriasis who continued therapy experienced resolution in 33.3% of cases (2/6). Of patients with generalized pustular psoriasis who discontinued therapy, 63.6% had improvement of symptoms and 27.3% had resolution of psoriasis at follow-up.

DISCUSSION

Psoriasiform lesions are a well documented complication of TNFα inhibitor therapy which can occur at any time during the treatment course.[2] However, in our analysis, we found the majority (69.9%) to occur within the first year of treatment. Furthermore, our review of published photographs suggests that many patients had generalized involvement with more than one morphological type. The typical presentations include plaque or palmoplantar pustular psoriasis, though various clinical morphologies have been reported. Severe scalp psoriasis associated with alopecia is a less common presentation observed in de novo psoriasis and the onset in a patient undergoing TNFα inhibitor therapy should prompt consideration of TNFα inhibitor-induced psoriasis.

The majority of the TNFα inhibitor-induced psoriasis biopsy samples were histologically indistinguishable from de novo psoriasis. However, in a study investigating histopathologic changes in TNFα inhibitor-induced psoriasiform clinical lesions, the authors concluded that the reactions comprise a spectrum ranging from that closely mimicking psoriasis, a sterile pustular folliculitis, or a lichenoid pattern.[3] The presence of eosinophils may also be suggestive of TNFα inhibitor-induced psoriasiform dermatitis.[3] A biopsy may be helpful in patients with new-onset psoriasis while on TNFα inhibitors to evaluate for these specific features. Biopsy may also be helpful in distinguishing TNFα inhibitor-induced psoriasis from lichenoid drug reaction, as both can present with clinically psoriasiform lesions. There are fewer reported TNFα inhibitor-induced lichen planus cases in the literature;

however, the prognosis is comparable to TNFα inhibitor-induced psoriasis such that most patients completely resolved following agent continuation or withdrawal with concomitant skin-directed treatment.[4]

In this study we found that more patients had resolution of symptoms after discontinuing TNF therapy (47.7%) compared to those who continued therapy (32.9%). While the majority of patients switching to a different TNFα inhibitor had either resolution (36.7%) or improvement (18.4%) in psoriasis, 44.9% experienced no improvement or recurrence, suggesting a need for additional treatment options in these patients.

The management approach may also vary depending on the clinical presentation. In patients with more severe presentations, such as generalized pustular psoriasis, only 27.3% of patients who discontinued therapy had resolution compared to 47.7% of all patients analyzed in systematic review who discontinued therapy. However, 63.6% of patients with generalized pustular psoriasis showed improvement, but not resolution, after discontinuing therapy. Therefore, such patients may need counseling on realistic expectations on the outcome and the probability that they may experience improvement rather than complete resolution of symptoms after discontinuing therapy. In contrast, half of the patients with alopecia had resolution of symptoms despite continuing or discontinuing therapy, albeit a larger quantity of patients were managed with discontinuation of therapy. These results suggest that patients may have different outcomes based on clinical subtype of psoriasis. While the number of patients with alopecia or generalized pustular psoriasis who switched to a different TNFα agent was small, all had either resolution or improvement of symptoms, which suggests that this may be a reasonable therapeutic approach in a subset of patients.

The prevalence of new-onset psoriasis in patients treated with TNFα inhibitors is unknown. The underlying disease itself may play a predisposing role, as patients with chronic rheumatologic and gastrointestinal inflammatory diseases have a higher incidence of psoriasis.[5,6] Immune dysregulation related to immunosuppression may additionally contribute; the prevalence of TNFα inhibitor-induced psoriasis in patients with RA and spondyloarthropathy (2.3–5%) [7–9] is similar to that in HIV disease (1.3–1.5%).[10] However, the temporal relationship between TNFα inhibitor and psoriasis onset (most often in the first year after exposure) supports a causal association. Overall the data suggest that TNFα inhibitor-induced psoriasis is a class effect, as this adverse reaction has been observed with all TNFα inhibitors and with all diseases for which TNFα inhibitors are indicated.[9,11]

While the exact mechanism of TNFα inhibitor-induced psoriasis remains elusive, emerging evidence suggests that the IL-23/T_H17 axis plays an important role in the pathogenesis.[12] IL-23 is a proinflammatory cytokine that drives downstream T_H1 and T_H17 effector responses, which have been implicated in the pathogenesis of chronic inflammatory diseases.[13] Genome-wide association studies have associated specific polymorphisms in the IL-23R gene with increased susceptibility to both CD and psoriasis.[14,15] In a study evaluating TNFα inhibitor-induced psoriasis in pediatric patients with CD, those who developed psoriasis were more often homozygous for three specific IL-23R polymorphisms compared to disease-matched controls who did not develop psoriasis following TNFα inhibitor treatment.[16] Similarly, adult patients with severe TNFα inhibitor-induced psoriasis

and psoriatic alopecia were homozygous wildtype carriers for a rare IL-23R variant.[17] Consistent with molecular studies, IL-12/23 antagonism with ustekinumab has been an effective treatment in several CD patients who developed TNFα inhibitor-induced psoriasis.[17,18] In addition, IL-23 regulates T_H17 cells, which secrete IL-17, a cytokine known to play a critical role in psoriasis. IL-17 serum and lesional levels in plaque and pustular psoriasis are higher compared to controls.[19] Furthermore, IL-17-expressing T cell infiltrates have been identified in TNFα inhibitor-induced psoriatic lesions.[17,20] In a study by Tillack et al, patients with CD who required transition to ustekinumab expressed high levels of infiltrating IL-17A+ cells.[17] While ustekinumab is not currently FDA approved for CD, clinical trials have shown promising results.[21–23] This data suggests that IL-23 and/or IL-17 antagonism may benefit a patient subset with severe TNFα inhibitor-induced psoriasis.

Disequilibrium in proinflammatory cytokine interferon alpha (IFNα) levels in the setting of TNFα suppression is also thought to contribute to psoriatic lesion development.[24–26] TNFα normally attenuates IFNα levels, therefore TNFα inhibition results in elevated IFNα. IFNα stimulates T_H1 lymphocytes, which play a role in the pathogenesis of psoriasis.[27] Furthermore, patients with hepatitis who developed psoriasis during IFNα treatment demonstrated regression of psoriatic lesions following IFN agent withdrawal.[28,29] Moreover, increased IFNα expression has been demonstrated in lesional dermal vasculature in patients with TNFα inhibitor-induced psoriasis.[24] Therefore, IFNα dysregulation may contribute to the pathogenesis of TNFα inhibitor-induced psoriasis.

The primary limitation of this review was variations in data presented in the reviewed publications. Not all authors performed biopsies or disclosed treatment approach or outcome. In addition, the follow-up interval varied among papers and may not truly represent the eventual clinical outcome. Furthermore, the long latency period between TNFα inhibitor initiation and psoriasis onset does not exclude the possibility of de novo psoriasis onset occurring independently of TNFα inhibitor therapy. The data is limited by the retrospective nature and reliance on case reports and small case series. Patients with inflammatory bowel or rheumatologic disease requiring TNFα inhibitor therapy are at risk for progression of disease if effective medications are discontinued after development of psoriasis. Identifying genotypical or phenotypical features of disease or risk factors for development of TNFα inhibitor-induced psoriasis may allow us to risk stratify patients. For example, with inflammatory bowel disease, the majority of patients reported to develop psoriasis had CD rather than UC, which may be due to the stronger association of CD and psoriasis with *IL23R* and *IL12B* gene variants than is observed with UC as discussed above. In addition, the majority of affected patients are female. Beyond that, with case reports and case series, only features of affected patients are presented, and it is not clear whether there is a difference in disease location, phenotype, or activity between patients who develop psoriasis and those who do not.

CONCLUSION

The paradoxical development of psoriasis can be an unintended consequence of TNFα antagonism. TNFα inhibitor cessation may result in resolution of induced psoriasis in

nearly half the cases, but there is still a substantial proportion of patients for whom lesions may persist. Decisions regarding interruption of anti TNFα therapy should be carefully considered in light of the possibility of psoriasis persistence and possible loss of efficacy for rheumatologic or gastrointestinal disease with cessation, should rechallenge become necessary. Thus, an initial approach of “treating through” with typical skin-directed therapies is reasonable except in the most severe cases. Further research is needed to clarify optimal strategies and clinical outcomes based on different clinical subtypes. While much remains to be learned about the mechanism of TNFα-induced psoriasis, emerging data on specific IL23R genetic polymorphisms have revealed potential therapeutic targets for patients with severe disease.

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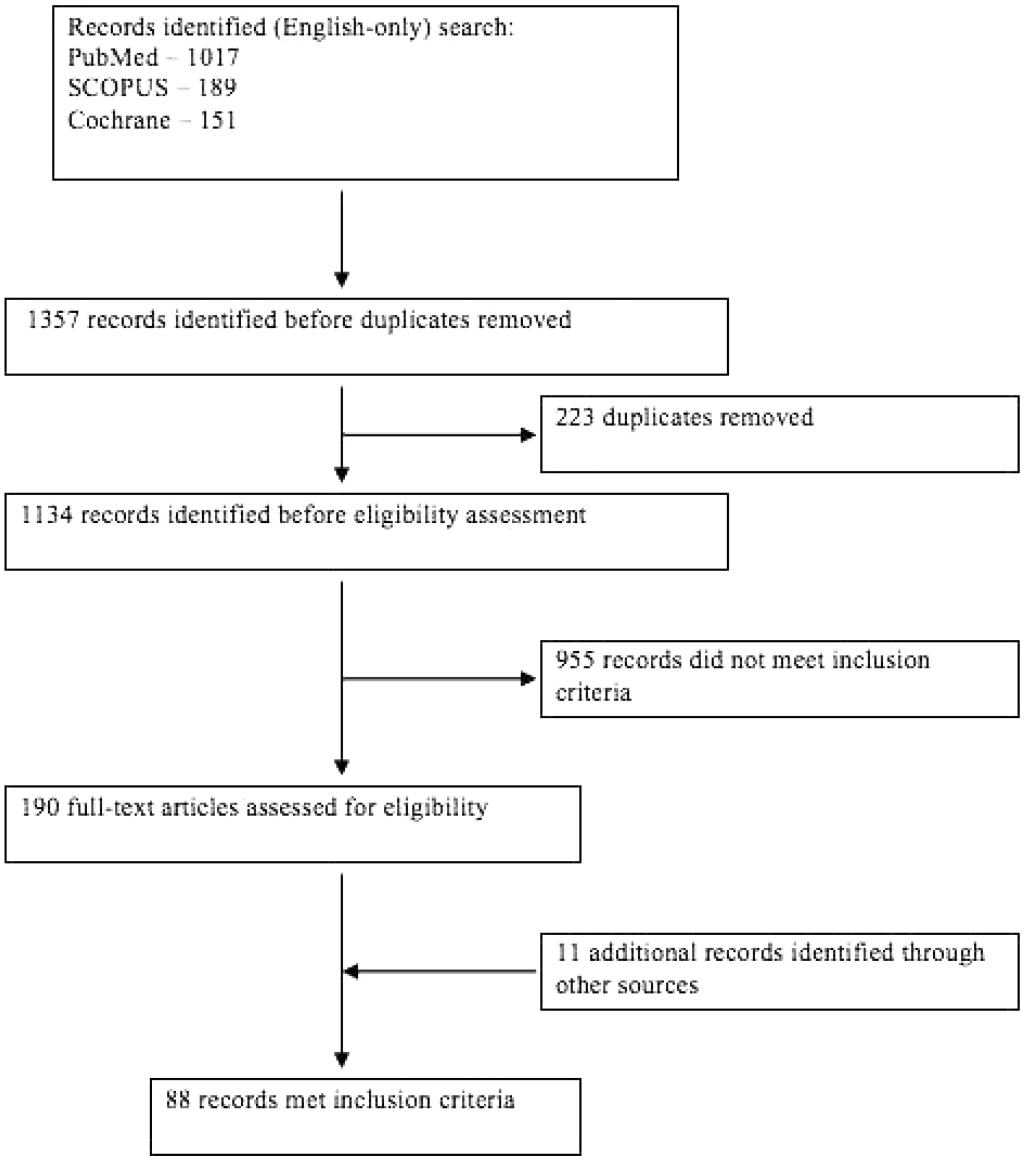

Figure 1:
The electronic search, selection and exclusion of studies in the systematic review.

Table 1:

Summary of demographic features of patients with TNFα inhibitor-induced psoriasis

Demographic Characteristics	Patients (N = 216) Patients (N = 216)
Gender, N (%)	
Female	156 (72.2)
Male	60 (27.8)
Average age, years (range)	38.5 (7–83)
Family history of psoriasis, N (% of 161 reported)	19 (11.8)
Primary disease, N (%)	
Crohn's Disease	88 (40.7)
Rheumatoid arthritis	80 (37.0)
Ankylosing spondylitis	30 (13.9)
Ulcerative colitis	6 (2.8)
Juvenile idiopathic arthritis	5 (2.3)
Behcet's disease	3 (1.4)
Spondylarthropathy	5 (2.3)
Synovitis, acne, pustulosis, hyperostosis, osteitis (SAPHO)	2 (1.0)
Bilateral idiopathic panuveitis	1 (0.5)
Inflammatory arthritis	1 (0.5)
TNF-alpha inhibitor resulting in psoriasis eruption, N (%)	
Infliximab	135 (62.5)
Adalimumab	47 (21.8)
Etanercept	31 (14.4)
Certolizumab	2 (1.0)
Golimumab	1 (0.5)
Concomitant immunomodulators, N (% of 95 reported)	
Methotrexate	32 (33.7)
Azathioprine	18 (18.9)
Leflunomide	13 (13.7)
Sulfasalazine	7 (7.4)
Hydroxychloroquine	2 (2.1)
6-mercaptopurine	2 (2.1)
Mesalazine	2 (2.1)
Cyclosporine	1 (1.0)
Tacrolimus	1 (1.0)
Concomitant systemic steroids, N	17
Clinical latency to eruption, months (range in months)	
Infliximab	13.6 (1–120)
Adalimumab	14.4 (1–62)
Etanercept	16.2 (2–72)
Certolizumab	5.0 (4–6)
Golimumab	4.0 (4; N=1)

Demographic Characteristics	Patients (N = 216) Patients (N = 216)
Morphology of skin lesions, N (%)	
Plaque	90 (44.8)
Palmoplantar pustular psoriasis	73 (36.3)
Psoriasiform	40 (19.9)
Severe alopecia	15 (7.5)
Generalized pustular	22 (10.9)
Guttate	16 (8.0)
Inverse	7 (3.5)
Follicular	2 (1.0)
More than one form	54 (26.9)
Body areas involved, N (%)	
Soles	99 (45.8)
Extremities	98 (45.4)
Palms	97 (44.9)
Scalp	78 (36.1)
Trunk	70 (32.4)
Face	19 (8.8)
Axillae	15 (6.9)
Groin	14 (6.5)
Not specified	20 (9.3)
Histology of lesions, N (% of 102 reported)	
Classic	56 (54.9)
Pustular PSO	34 (33.3)
Psoriasiform dermatitis	12 (11.8)
Psoriatic treatment, N (% of 204 reported)	
Topical steroids	156 (76.5)
Vitamin D Analogue	36 (17.6)
Methotrexate	35 (17.2)
Systemic steroids	19 (9.3)
Phototherapy	17 (8.3)
Cyclosporine	11 (5.4)
Acitretin	4 (2.0)
Coal tar	2 (1.0)
Unknown	12

Table 2:

Summary of therapeutic management and outcomes of patients with TNFα inhibitor-induced psoriasis

	Total	Infliximab	Adalimumab	Etanercept	Golimumab	Certolizumab
Continued on TNF therapy (N)	82	55	14	12	1	-
Resolved (%)	27 (32.9)	22 (40.0)	1 (7.1)	4 (33.3)	-	-
Improved (%)	47 (57.3)	30 (54.5)	12 (85.7)	4 (33.3)	1 (100.0)	-
No improvement (%)	8 (9.8)	3 (5.5)	1 (7.1)	4 (33.3)	-	-
Discontinued offTNF therapy (N)	65	32	19	12	-	2
Resolved (%)	31 (47.7)	17 (53.1)	10 (52.6)	3 (25.0)	-	1 (50.0)
Improved (%)	30 (46.2)	12 (37.5)	8 (42.1)	9 (75.0)	-	1 (50.0)
No improvement(%)	4 (6.2)	3 (9.4)	1 (5.3)	-	-	-
Switched to different TNF agent (N)	49	9	19	18	-	3
Resolved/no recurrence at follow-up	18 (36.7)	2 (22.2)	8 (42.1)	7 (38.9)	-	1 (33.3)
Improved	9 (18.4)	2 (22.2)	2 (10.5)	4 (22.2)	-	1 (33.3)
No improvement	22 (44.9)	5(55.6)	9 (47.4)	7 (38.9)	-	1 (33.3)

Table 3:

Summary of outcomes with severe presentations including alopecia and/or generalized pustular psoriasis

Clinical subtype*	Clinical Outcome	Continued TNF therapy	Discontinued TNF therapy	Switched to different TNF agent
Alopecia	Resolved	2/4 (50.0%)	4/8 (50.0%)	
	Improved	1/4 (25.0%)	2/8 (25.0%)	1/1 (100.0%)
	No improvement	1/4 (25.0%)	2/8 (25.0%)	
	Unknown (N=2)			
Generalized pustular psoriasis	Resolved	2/6 (33.3%)	3/11 (27.3%)	2/4 (50.0%)
	Improved	2/6 (33.3%)	7/11 (63.6%)	2/4 (50.0%)
	No improvement	2/6 (33.3%)	1/11 (9.1%)	
	Unknown (N=1)			

*Note that 3 patients had both alopecia and generalized pustular psoriasis