Case Report

Anti-Tumor Necrosis Factor-α-Induced Psoriasis

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ABSTRACT. We describe a patient with rheumatoid arthritis who developed psoriasis during treatment with etanercept; psoriatic lesions resolved completely after the drug was discontinued, but returned on rechallenge. No such adverse skin reaction occurred after switching therapy to infliximab. Through a Medline search we identified 11 reports involving 32 patients who developed psoriasis/psoriasiform eruptions during therapy with tumor necrosis factor-α (TNF-α) inhibitors. All TNF-α blocking agents have been reported to lead to or exacerbate psoriasis. In some cases skin changes were severe enough to discontinue the medication. (J Rheumatol 2006;33:1411–4)

Key Indexing Terms:
TUMOR NECROSIS FACTOR-α INHIBITORS PSORIASIS ADVERSE EFFECT

Anti-tumor necrosis factor-α (TNF-α) drugs have given new insights in the treatment of rheumatic diseases, including rheumatoid arthritis (RA), ankylosing spondylitis, Crohn's disease, psoriatic arthritis, and psoriasis[1,2]. At present, 3 anti-TNF-α biological response modifiers are available: etanercept (ETA; Enbrel®, Wyeth), infliximab (INF; Remicade®, Schering-Plough), and adalimumab (ADA; Humira®, Abbott). However, there are some safety concerns with these agents, essentially involving infection[3]. Recently, all TNF inhibitors have paradoxically been reported to induce psoriasis[4,5].

We describe a patient with RA who developed psoriasis during treatment with ETA, whose psoriatic lesions resolved completely after the drug was discontinued, but returned on rechallenge. No such adverse skin reaction occurred after switching to INF. We also review published case reports of psoriasis and psoriasiform eruptions during anti-TNF-α therapy in the English language literature.

CASE REPORT

A 30-year-old woman who had been diagnosed with RA 3 years before[6] presented with well demarcated erythematous, scaly, papular, and pruritic eruptions over the scalp, elbows, abdomen, and lower back. During the last 6 months, her disease had been active despite therapy with a combination of hydroxychloroquine (400 mg/day), methotrexate (MTX; 20 mg/wk subcutaneously), and leflunomide (20 mg/day). Because of this, ETA 50 mg/week had been started 2 months before. She denied any personal or family history of psoriasis or inflammatory back pain. There was no distal interphalangeal joint involvement or clinical evidence of psoriasis or psoriasiform skin/nail lesions. Concomitant medications at the time included prednisone 6 mg/day, MTX 10 mg/week, and diclofenac 150 mg/day. Laboratory tests were negative for antinuclear antibody and rheumatoid factor (RF). She was negative for HLA-B27. Skin biopsy taken from the lower back revealed confluent parakeratosis, psoriasiform hyperplasia, acanthotic epidermis with regular elongation of rete ridges, suprapapillary thinning, and dilatation of superficial dermal capillaries with an infiltrate of neutrophils in the upper dermis; psoriasis was diagnosed. Because of an inadequate response to topical corticosteroid treatment, ETA was discontinued: the skin lesions resolved completely within 10 days. However, her arthritic symptoms recurred after one month; ETA had to be restarted, with recurrence of the psoriatic eruptions after the first injection. Withdrawal of ETA therapy again resulted in prompt resolution of the skin lesions. Two months later, she was started on INF, with good clinical response, and with no recurrence of psoriatic lesions in a followup of 7 months.

DISCUSSION

We describe a case of new-onset psoriasis vulgaris in a female patient with RA during treatment with ETA. The diagnosis was confirmed by histopathological examination. Although she was seronegative for RF, clinical and radiographic features were consistent with RA and she fulfilled the American College of Rheumatology criteria for RA[6]. Negative personal and family history in a first-degree relative makes the diagnosis of psoriatic arthritis unlikely[7].

A number of drugs can induce exacerbation of preexisting psoriasis or lead to development of psoriasis or psoriasiform eruptions in patients with no history of such conditions. Psoriasiform eruptions are similar to idiopathic psoriasis and typically consist of erythematous plaques covered by large dry silvery scales. Their distinction from psoriasis vulgaris is sometimes difficult and can be made based on histological characteristics. The histopathological findings in these cases are various and in general, features of psoriasis vulgaris are combined with those of drug eruptions or of chronic dermatitis[8].

Antimalarial drugs are well known to induce exacerbation of psoriasis, but our patient had discontinued all medications except for MTX and diclofenac before the start of biologic therapy[8]. Nonsteroidal antiinflammatory drugs are also known to be associated with the development of psoriasis or

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its exacerbation[9]. However, our patient had been taking diclofenac for nearly 3 years with no adverse effect on the skin. Disappearance of lesions after discontinuation of ETA and recurrence after the rechallenge implicates this agent in causing the development of psoriasis in our patient.

Through a Medline search we identified 11 reports involving 32 patients who developed psoriasis/psoriasiform eruptions during therapy with TNF-α inhibitors[4,5,10-18]. The demographic and clinical features of these patients are presented in Table 1. Development or exacerbation of psoriasis or psoriasiform skin eruptions was reported with all 3 TNF inhibitors (8 with ETA, 14 with INF, 10 with ADA)[4,5,10,12-17]; but exacerbation of psoriasis was more commonly reported with ETA, whereas new-onset psoriasis and psoriasiform skin eruptions were reported more frequently with INF and ADA[11,16,18]. Mean ages of the patients were similar for all agents (Kruskal-Wallis test 5.3, DF 2, p = 0.07), but the mean interval between the onset of the adverse event and the administration of TNF-α antagonist seems to be different across the 3 TNF inhibitors (Kruskal-Wallis test 6, DF 2, p = 0.048; Table 2). Withdrawal of TNF-blocking agents led to improvement of psoriatic lesions in almost all cases (Patients 2, 5, 6, 9, and 27), and rechallenge resulted in recurrence of psoriasis (Patients 12, 13, and 16). If the same anti-TNF antagonist was continued, psoriatic lesions were more likely to persist (Patients 1, 3, 4, 11, 14, 17, 19, 20, 22, 26, 30, and 32); resolution was observed only in a few cases (Patients 25, 28, and 29).

In our patient, psoriasis developed shortly after the first ETA injection, and recurred promptly upon rechallenge, but did not relapse after the start of INF treatment during a followup of 7 months. Switching to another TNF inhibitor was tried in 4 of the published cases for different reasons (Table 3). Despite the change of initial biologic treatment, psoriatic lesions relapsed in 2 patients (Patients 10, 15), whereas no recurrence was observed in another patient (Patient 23). One patient developed psoriasis under INF and ADA, but not dur-

Table 1. Characteristics of the patients who developed psoriasis/psoriasiform eruption or exacerbation during biological treatment.

Patient	Age/Sex	Diagnosis	Treatment	Latency, mo	Adverse Event	History	Family Data	Histopathology	Reference
1	36 M	UC	INF	6	NoPs	–	–	+	12
2	63 F	RA	ADA	3	PsE	–	NA	ND	10
3	47 F	RA	INF	2	NoPs	–	–	+	17
4	55 F	RA	ETA	3	NoPs	–	–	+	17
5	NA	RA	ADA	9	PsE	NA	NA	+	16
6	NA	RA	ADA	48	NoPs	NA	NA	+	16
7	NA	RA	ADA	16	NoPs	NA	NA	+	16
8	NA	PsA	INF	NA	EPs	+	NA	+	16
9	46 F	CD	INF	0.5	PsE	–	NA	+	11
10	33 F	AS	INF	9	NoPs	–	–	+	5
11	65 F	RA	ADA	9	NoPs	–	–	+	5
12	49 M	BD	INF	6	NoPs	–	–	+	5
13	43 M	BD	INF	7	NoPs	–	–	ND	5
14	48 F	RA	ETA	7	NoPs	–	–	+	5
15	41 F	RA	ADA	23	NoPs	–	–	+	4
16	69 F	RA	ETA	1	EPs	+	–	+	4
17	65 F	RA	ADA	4 days	NoPs	–	–	+	4
18	38 M	RA	INF	3	EPs	+	+ (sister)	ND	4
19	67 F	RA	ADA	5	NoPs	–	+ (brother)	+	4
20	49 F	RA	INF	8	EPs	+	–	ND	4
21	49 F	RA	ETA	1	EPs	+	–	ND	4
22	63 F	RA	ETA	2	NoPs	–	–	ND	4
23	40 F	RA	ADA	11	NoPs	–	–	ND	4
24	32 M	AS	INF	1.5	NoPs	–	NA	NA	13
25	27 F	AS	INF	10	NoPs	–	NA	NA	13
26	25 M	AS	ETA	7	EPs	+	NA	NA	13
27	34 F	AS	ETA	4	EPs	+	NA	NA	13
28	NA	SpA	INF	2	PsE	–	–	+	18
29	NA	SpA	INF	8.5	PsE	–	–	+	18
30	NA	SpA	INF	5.6	PsE	–	–	+	18
31	NA	Ps	ETA	NA	EPs	+	NA	NA	15
32	37 F	RA	INF	9.5	NoPs	+	–	NA	14
33	30 F	RA	ETA	2	NoPs	–	–	+	Present case

RA: rheumatoid arthritis, UC: ulcerative colitis, PsA: psoriatic arthritis, CD: Crohn's disease, BD: Behçet's disease, INF: infliximab, ADA: adalimumab, ETA: etanercept, NA: not available, Latency: interval between administration of anti-TNF agent and onset/exacerbation of psoriasis or psoriasiform eruption, SpA: spondyloarthropathy, Ps: psoriasis, History: history of psoriasis, Family Data: family history of psoriasis, NoPs: new-onset psoriasis, PsE: psoriasiform eruption, EPs: exacerbation of psoriasis, ND: not done.

Table 2. Characteristics of subjects that developed psoriasis/psoriasiform skin changes during biological therapy. Data are means ± SD.

	INF	ETA	ADA	Total
No. of patients	14	9	10	33
Age, yrs	40 ± 8	47 ± 16	57 ± 13	46 ± 13
Primary disease, no.				
RA	4	6	9	19
AS + SpA	6	2	—	8
Ps + PsA	—	1	1	2
IBD	2	—	—	2
BD	2	—	—	2
Latency, mo	5.6 ± 3.2	3.3 ± 2.4	13.7 ± 14.5	7.4 ± 8.9
Personal history of psoriasis, %	14.3	55.6	10	24.2
Family history of psoriasis, %	7	0	10	6.1
Development of new onset psoriasis, %	57.1	44.4	70	57.6
Exacerbation of psoriasis. %	14.3	55.6	10	24.2
Psoriasiform eruptions, %	28.6	—	20	18.2

RA: rheumatoid arthritis, AS: ankylosing spondylitis, SpA: spondyloarthropathy, Ps: psoriasis, PsA: psoriatic arthritis, IBD: inflammatory bowel disease, BD: Behçet's disease, INF: infliximab, ETA: etanercept, ADA: adalimumab, Latency: interval between administration of anti-TNF agent and onset/exacerbation of psoriasis or psoriasiform eruption.

Table 3. Psoriasis/psoriasiform skin changes during treatment with different anti-TNF agents.

	Patient 10	Patient 15	Patient 18	Patient 23	Present Case
Agent 1/AE/latency	INF/+/9 mo	ADA/+/23 mo	INF/+/3 mo	ADA/+/11 mo	ETA/+/2 mo
Agent 2/AE/latency	ETA/RS	ETA/+/3 wks	ETA/–/–	INF/–/–	INF/–/–
Agent 3/AE/latency	—	INF/+/after second infusion	ADA/+/6 wks	—	—
Agent 4/AE/latency	—	ETA/RS	—	—	—
Purpose of changing therapy	INF = severe psoriasis	ADA = severe psoriasis; ETA = temporarily unavailable; INF = patient's refusal	INF = insufficient anti-rheumatic effect; ETA = insufficient anti-rheumatic effect	ADA = severe psoriasis	ETA = severe psoriasis + patient's refusal

AE: adverse event (psoriasis), INF: infliximab, ETA: etanercept, ADA: adalimumab, latency: interval between administration of anti-TNF agent and onset/exacerbation of psoriasis or psoriasiform eruption, RS: lesions persisted but remained stable.

ing treatment with ETA (Patient 18). However, lesion-free followup time after switching was not reported in this and other cases. The time interval in our patient and in some of these cases may not be long enough for a recurrence, because the mean intervals for the development of psoriatic lesions with INF (5.6 ± 3.2 months) and ADA (13.7 ± 14.5 months) are longer than with ETA (3.3 ± 2.4 months).

TNF inhibitors have been well documented for benefit in the treatment of psoriasis[19]. Thus, it is quite perplexing that psoriasis can also develop or may be aggravated as an adverse effect during therapy with these agents. In a recent report describing 5 cases some possible mechanisms for development of psoriasis have been proposed, such as the activation of autoreactive T cells leading to tissue damage or activation of a cutaneous lymphocyte antigen-expressing T cell subset and increase in the expression of chemokine receptors, such as CXCR3, which both promote infiltration of autoreactive T cells to the skin[5]. A role for bacterial infections has also been suggested[4], but no mention was made of preceding bacterial infection in the reported cases. Despite these hypotheses, the pathogenic mechanism of this paradoxical adverse event is still unclear.

ETA binds and neutralizes soluble and membrane-bound TNF-α as well as a related molecule, lymphotoxin-α. In addition, binding of ETA to TNF-expressing cells does not result in cell lysis in the presence or absence of complement. In contrast, INF and ADA are both monoclonal antibodies with potential to cause cell lysis via antibody-dependent cell-mediated cytotoxicity. Although both agents are specific for TNF, they do not bind lymphotoxin-α[20].

Our review based on disparate cases in the literature suggests there may be differential effects of ETA and INF or ADA on the occurrence of psoriasis. This difference can probably not be explained by the aforementioned molecular dissimilarities between these agents. A recent report described upregulation of interferon-γ (IFN-γ) and TNF-α by T cells from ETA-treated patients with ankylosing spondylitis, and indicated that efficient neutralization of soluble TNF is possible

without interfering with the ability of the T cells to produce TNF-α and IFN-γ[21]. A parallel study using the same methodology showed that secretion of both cytokines is downregulated in INF-treated patients[22]. If these findings are confirmed by others, the opposite effects of ETA and INF on the regulation of IFN-γ secretion by T cells may offer an attractive explanation for the differential effect of these agents on psoriasis, at least in some patients, given the evidence in the literature to support the concept that psoriasis is a type 1 autoimmune disease, primarily mediated by IFN-γ[23]. Upregulation of local TNF secretion by T cells may also be contributing to the process, as it also plays an important and probably synergistic role with IFN-γ[23].

In summary, psoriasis can develop during therapy with each of the anti-TNF agents that may sometimes be severe enough to discontinue the medication. Onset/exacerbation of psoriasis is not always a class effect, thus switching to another TNF inhibitor should be considered in appropriate cases. The latency period for this adverse effect is quite variable and may sometimes be delayed up to a few years after exposure. Although the exact incidence and prevalence of this undesirable event is unknown, increasing numbers of reports indicate that it is not rare. Future studies may shed light on the differences of the TNF inhibitors with respect to their psoriatic adverse effects and the underlying pathogenetic mechanisms.

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