

# A Mechanism-Based Classification of Dermatologic Reactions to Biologic Agents Used in the Treatment of Cutaneous Disease: Part 2

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**Biologic therapies are an efficacious new method of controlling a number of chronic conditions. Data regarding these medications continues to emerge, giving clinicians a greater understanding of their side effects profiles. The biologic agents used in dermatology, particularly the tumor necrosis factor- $\alpha$  inhibitors, have a number of varied dermatologic side effects. In this two-part article, we perform a review of literature regarding cutaneous side effects of infliximab, etanercept, adalimumab, rituximab, efalizumab, and alefacept. In this second part, we discuss injection site reactions, infusion reactions, vasculitis, drug-induced lupus erythematosus, psoriasiform lesions, rebound phenomenon, eczema, atopic dermatitis, and hypersensitivity reactions**

**I**N THIS SECOND PORTION of our review of the cutaneous side effects of biologic agents, we will explore those reactions that are of an immune nature. While we again group the tumor necrosis factor- $\alpha$  (TNF- $\alpha$ ) inhibitors (infliximab, etanercept, and adalimumab) for their tendency toward class effect, infliximab does have a somewhat different profile, likely due to its chimeric murine/human design. This particularly manifests itself in the development of antinuclear antibodies (ANAs).

Using PubMed, we reviewed the literature for publications that reported cutaneous side effects during the use of infliximab, etanercept, adalimumab, rituximab, efalizumab, and alefacept in order to summarize the prevalence of any suspected induced dermatologic conditions associated with these medications. In this article, we discuss injection site reactions, infusion reactions, vasculitis, drug-induced lupus erythematosus, psoriasiform lesions, rebound phenomenon, eczema, atopic dermatitis, urticaria, erythema multiforme, Stevens-Johnson syndrome, and toxic epidermal necrolysis.

## Infusion Reactions and Injection Site Reactions

An infusion reaction (IR) is defined as any adverse event occurring within a specific window of time around infusion; definitions vary between within 2 hours of infusion,<sup>1</sup> to within 24 hours of infusion.<sup>2</sup> As their only unifying characteristic is time frame, IRs are variable and can consist of pruritus, urticaria, irregularities in blood pressure or heart rate, chills or fevers, and anaphylaxis. In initial clinical trials of 6,443 patients treated for rheumatoid arthritis (RA) and Crohn's disease (CD) with infliximab, rates of IR were 20% (vs 9% for placebo).<sup>1</sup> Further trials have yielded wide-ranging results for rates of IR. In the treatment of RA, rates ranged between 3% (vs 2% for placebo  $n = 340$ )<sup>3</sup> and 21% (no placebo rate available,  $n = 213$ ).<sup>4</sup> For CD, rates of acute IR varied between 3.8% (no placebo available,  $n = 500$ )<sup>5</sup> and 24% (no placebo available,  $n = 129$ ).<sup>6</sup>

Currently available data regarding pretreatment are inconclusive. Many patients develop antibodies to infliximab, which have been linked to decreased efficacy of the drug<sup>7</sup> as well as to possible increased rates of IRs.<sup>8</sup> Studies looking at pretreatment with corticosteroids to decrease the rate of antibody production and studies looking at pretreatment to decrease the rate of IRs are summarized in Table 1. Pretreatment tends to *increase* rates of IR; however, this is likely due to the side effects of the pretreatment drugs themselves. Additionally, likely the single best way to avoid severe IR is with regular treatment. Administration of a second dose of infliximab is strongly associated with a decreased rate of developing antibodies.<sup>9</sup>

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**Table 1.** Pretreatment for Infusion Reaction from Infliximab

Study	Design	Findings	Statistical Significance
Farrell RJ et al <sup>9</sup>	80 CD patients randomized to receive 200 mg IV hydrocortisone or placebo immediately before their first and subsequent infusions; endpoint being decreased numbers of antibodies to infliximab	At week 16, levels of antibodies were lower in the treatment group.	1.6 vs 3.4 µg/mL, $p = .02$
Sany J et al <sup>80</sup>	355 RA patients randomized to betamethasone 0.15 mg/kg 30 min before infliximab infusion or placebo for 36 weeks, endpoint being tolerance of infusions	Twice as many infusions in the treatment group resulted in IRs as in the placebo group.	840 infusions with 5% incidence, vs 827 infusions with 2.5% incidence in placebo ( $p = .05$ )
Wasserman MJ et al <sup>81</sup>	Retrospective analysis of 113 patients with RA receiving a total of 1,183 infusions; data analyzed for infusion reactions in patients pretreated with antihistamine vs no pretreatment	Reactions occurred in 13.2% of patients undergoing pretreatment vs 7.5% of those with no pretreatment.	—
Jacobstein DA et al <sup>82</sup>	Retrospective analysis of 243 pediatric patients with IBD; data analyzed for infusion reactions in patients with and without pretreatment (antipyretic, antihistamine, or corticosteroid)	Reactions occurred in 12 of 33 patients with pretreatment vs 28 of 210 without pretreatment.	$p < .01$
Lequerre T et al <sup>12</sup>	Retrospective analysis of 203 patients being treated for RA and spondyloarthritis with goal of generating recommendations for management of IR	23 of 203 patients experienced IRs, including blood pressure abnormalities ( $n = 13$ ), sudden flushing ( $n = 9$ ), throat irritation, edema ( $n = 6$ ), urticaria ( $n = 6$ ), dyspnea ( $n = 5$ ), and nausea/vomiting ( $n = 3$ ).	Extensive algorithm proposed. Initial management consists of stopping infusion or slowing down to rate of 60 mL/hr and treating patient's symptoms as medically appropriate.

CD = Crohn's disease; IBD = inflammatory bowel disease; IR = infusion reaction; IV = intravenous; RA = rheumatoid arthritis.

Also, the use of episodic infliximab has been associated with 14% of adults developing severe systemic reactions (86 patients treated for CD).<sup>10</sup> Occasional incidents of anaphylaxis have been reported, including one of two patients treated for RA who developed type 1 reactions after not receiving infliximab for approximately 2 years.<sup>11</sup>

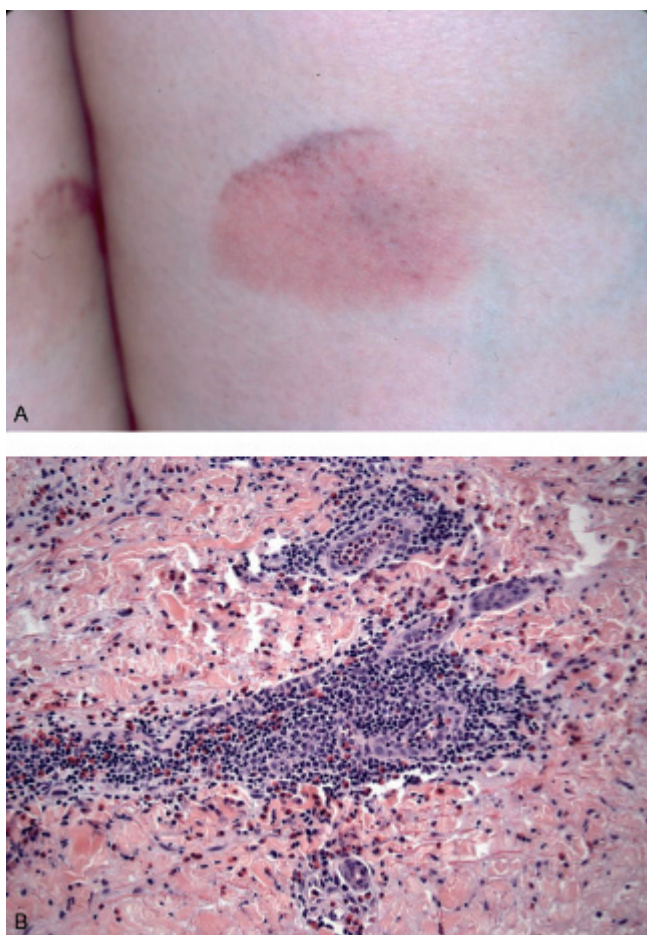
A study by Lequerre and colleagues attempted to establish a management protocol for infliximab-related IRs<sup>12</sup> that is summarized in Table 1. The publication proposed an extensive algorithm for management of IR; initial management consists of stopping infusion or slowing down to a rate of 60 mL per hour and treating the patient's symptoms as medically appropriate.

Injection site reaction (ISR), often defined as a constellation of symptoms including swelling, erythema, pruritus, and pain around the site of injection, remains the most common cutaneous side effect of the monoclonal antibodies (Figs 1A and 1B). The frequency of ISRs in numerous trials can be seen in Table 2. Of note, the

frequency of ISRs appears to vary depending on the disease being treated, the frequency in RA<sup>13</sup> being much higher than in psoriasis (PsO).<sup>14–16</sup>

ISRs from etanercept and adalimumab are reported as decreasing in frequency and intensity as the drug is continued.<sup>13,17</sup> However, case reports exist of patients whose administration site reactions continue to worsen.<sup>18,19</sup> Though not often reported, recall reactions (IRs that develop at prior injection sites) may often be associated with administration site reactions. In a study of IRs with etanercept, 8 of the 20 patients who developed IRs developed recall reactions<sup>18</sup> (Fig 2).

A study of IRs in the use of etanercept found that CD8<sup>+</sup> T lymphocytes were the most common cell type in both primary and recurrent IRs and subsequently concluded that this cell type is likely responsible for the delayed hypersensitivity reaction.<sup>18</sup> Typically, IRs can be limited by varying the site of injection. Cutaneous reaction of this variety is very rarely a reason for discontinuation of treatment.<sup>15</sup>



**Figure 1.** A, Injection site reaction (ISR) to etanercept. This patient was receiving etanercept therapy for rheumatoid arthritis. She developed a moderately severe injection site reaction. B, Histology of ISR reveals perivascular lymphocytes, dermal edema, and occasional eosinophils (hematoxylin-eosin stain;  $\times 200$  original magnification).

Regarding efalizumab, although IRs have been reported, they do not appear to be a significant side effect. Randomized trials have not reported a greater incidence than with placebo.<sup>19–22</sup>

With alefacept, the incidence of IRs has ranged between a rate of 7% of patients treated versus none reported with placebo<sup>23</sup> to 16% of patients treated versus 8% with placebo.<sup>24</sup>

### Cutaneous Vasculitis

Cutaneous vasculitis is not a side effect noted in clinical trials for any of the TNF- $\alpha$  inhibitors, but two noteworthy reports have been published since then, one being a review of Medline catalogued literature, the other being a survey of hospital-based internists and rheumatologists in France. An example of cutaneous vasculitis is depicted in Figure 3. The basic summaries of these studies are reported in Table 3.

Since this publication, two noteworthy studies have been done on this topic. The first is a review of literature between 1990 and December 2006 regarding autoimmune diseases associated with TNF- $\alpha$  inhibitor therapy,<sup>25</sup> the results of which are presented in Table 3. Of note in this study, of patients who continued to use the TNF- $\alpha$  inhibitor, 75% of cases resolved ( $n = 12$ ) whereas, when the TNF- $\alpha$  inhibitor was discontinued, 67% had complete resolution ( $n = 101$ ). Another significant report is from France, where 1,200 hospital-based rheumatologists and internists were surveyed to report cases of vasculitis with TNF- $\alpha$  inhibitor involvement,<sup>26</sup> the results of which are summarized in Table 3. Again, in this study, the six patients in which the TNF- $\alpha$  inhibitor was continued experienced a resolution of their symptoms.

Of note, TNF- $\alpha$  inhibitors have been used successfully for the *treatment* of vasculitis. There are reports of its successful use in the treatment of giant cell arteritis<sup>27</sup> and Churg-Strauss syndrome that was refractory to conventional therapies.<sup>28</sup> However, a trial in which etanercept was used as part of combination therapy in the treatment of Wegener's granulomatosis showed no significant benefit.<sup>29</sup>

### Drug-Induced Lupus Erythematosus

The use of TNF- $\alpha$  inhibitors has been linked to the development of systemic lupus erythematosus (SLE) and cutaneous lupus erythematosus (Fig 4). This effect was noted during the first clinical trials. Four of 2,292 patients developed SLE with infliximab treatment; in all four cases, the lesions resolved with discontinuation of the drug.<sup>1</sup> Also reported in clinical trials was one case of SLE among 2,334 cases treated with adalimumab.<sup>30</sup>

Two recently published review articles summarized the reports of drug-induced SLE from TNF- $\alpha$  inhibitors; the results can be found in Table 4. Also, we reviewed the published reports of cases of cutaneous lupus not reviewed in the article by Costa and colleagues,<sup>31–38</sup> the results of which can also be found in Table 4. Of interest, in the study by Ramos-Casals and colleagues, infliximab was associated with serositis far more than with the other TNF- $\alpha$  inhibitors (24% vs 3%,  $p = .008$ ). Cutaneous features were more greatly associated with the use of etanercept (44% vs 12%,  $p = .01$ ).<sup>25</sup>

It is noteworthy that the incidence of cutaneous involvement with the diagnosis of SLE associated with TNF- $\alpha$  inhibitors appears to be significantly higher—67%<sup>25</sup> to 73%<sup>39</sup>—than in other causes of drug-induced

**Table 2.** Rates of Injection Site Reactions Associated with Etanercept and Adalimumab

<i>TNF-<math>\alpha</math> Inhibitor</i>	<i>Disease Process</i>	<i>Study</i>	<i>Results</i>
Etanercept <sup>17</sup>	RA, PsA	Initial clinical trials of 1,440 patients with RA and 157 patients with PsA	37% in treatment group vs 10% in placebo group
Adalimumab <sup>30</sup>	RA	Initial clinical trials of 2,468 patients	20% in treatment group vs 14% in placebo group
Etanercept <sup>13</sup>	RA	Phase II randomized controlled trial of 234 patients receiving 25 mg twice weekly	49% in treatment group vs 13% of controls
Etanercept <sup>14</sup>	PsO	Randomized controlled trial of 311 patients receiving 50 mg twice weekly for 12 weeks	10.9% in treatment group vs 0.7% in placebo group (number of patients experiencing ISR)
Etanercept <sup>15</sup>	PsO	Randomized controlled trial of 583 patients randomized to 25 mg, 50 mg, or control for 12 weeks, followed by all subjects receiving the drug	18% in 50 mg group, 13% in 25 mg group, and 6% in placebo group*
Adalimumab <sup>83</sup>	PsA	Randomized controlled trial of 313 patients treated with 40 mg for 24 weeks	6.6% in treatment group vs 3.1% in placebo group
Adalimumab <sup>84</sup>	PsO	Randomized controlled trial of 1,212 patients treated for 15 weeks	3.2% in treatment group vs 1.8% in placebo group
Adalimumab <sup>85</sup>	RA	Phase III randomized double-blind trial of 544 patients randomized to adalimumab 20 mg every other week, 20 mg weekly, 40 mg every other week, 40 mg weekly, or placebo	9.7% of those receiving adalimumab, 0.9% of placebo group
Adalimumab <sup>86</sup>	CD	Trial of 854 patients wherein all patients received open-label induction therapy and were subsequently randomized to double-blind treatment with placebo, adalimumab 40 mg every other week, or adalimumab 40 mg weekly for 56 weeks	4.2% in treatment group vs 0.4% in placebo group

CD = Crohn's disease; ISR = injection site reaction; PsA = psoriatic arthritis; PsO = psoriasis; RA = rheumatoid arthritis; TNF- $\alpha$  = tumor necrosis factor- $\alpha$ .

\*Percentages represent reactions per injection.



**Figure 2.** Etanercept recall reaction in a patient with rheumatoid arthritis. During her first month of etanercept therapy, the patient regularly developed injection site reactions (ISRs) that typically resolved after 24 hours. This is an example of a recall reaction, in which a new ISR was accompanied by erythema of a previous ISR.

SLE (9–27% in patients treated with procainamide and hydralazine).<sup>40</sup>

Although drug-induced SLE related to anti-TNF- $\alpha$  therapy may be an uncommon occurrence, the induction of ANAs is very common. In clinical trials, 11% of those taking etanercept developed ANAs, versus 5% of those on placebo; similar results were found for adalimumab.<sup>17,30</sup> Initial trials of infliximab found that 62% of treated patients developed ANAs, versus 27% of those on placebo. Prospective trials done since then have confirmed the high rates of ANA development. A study by Louis and colleagues found that 76% of 42 patients being treated with infliximab developed new autoantibodies, including 45% developing ANAs and 33% developing anti-double-stranded deoxyribonucleic acid (dsDNA) antibodies.<sup>41</sup> Another study of infliximab found that, after 24 months, 71 of 125 had developed ANAs.<sup>42</sup> Notably in this study, two patients, both of whom were ANA and dsDNA positive, developed lupus. In this study, ANAs were associated with female gender ( $p = .024$ ) and a



**Table 3.** Summary of Studies on Cutaneous Vasculitis

<i>Study Type</i>	<i>Cases</i>	<i>Diseases Treated</i>	<i>TNF-<math>\alpha</math> Inhibitor</i>	<i>Presentation</i>	<i>Demographic Information</i>	<i>Histology</i>	<i>Treatment</i>	<i>Resolution</i>
Review of literature of 1990–2006 investigating autoimmune diseases associated with TNF- $\alpha$ inhibitor therapy <sup>25</sup>	113	RA (95) CD (7) JIA (5) PsA (3) AS (3)	E (59) I (47) A (5)	Cutaneous lesions (87%), purpura (57%), ulcerative lesions (9%), nodules (9%), digital vasculitis (6%), maculopapular rash (5%); visceral vasculitis observed in 24% (peripheral nerve and renal involvement were the most common)	Available for 98 cases: 79 women, 19 men Average age: 51 Average time to onset: 38 weeks	Leukocytoclastic vasculitis (63%), necrotizing vasculitis (17%), lymphocytic vasculitis (6%)	Corticosteroids, 25%; other immunosuppressants, 15%	Offending agent withdrawn in 101 cases. Among cases continued, 9 resolved, 3 did not. In discontinued patients, complete resolution in 67, partial improvement in 25, and no resolution in 8.
Survey of 1,200 hospital-based rheumatologists and internists in France regarding cases of vasculitis with TNF- $\alpha$ inhibitor involvement <sup>26</sup>	39	RA (34) JIA (2) AS (2) PsA (1)	E (21) I (15) A (2) an investigational drug not specified (1)	Cutaneous involvement (33), purpura (10), nodules (8), necrotic plaques (8), blisters (3), erythrocytosis (3), chilblains (2), livedo (2); visceral involvement primarily in peripheral nervous system and kidneys	32 women, 7 men Average age: 51.6 years Average time to onset: 9.6 months (range, 0.5–80 months)	Available in 22: leukocytoclastic vasculitis (12), necrotizing vasculitis (7), inflammatory infiltrate of the dermis without evidence of vasculitis (3)	14 given high-dose corticosteroids or immunosuppressants 14 were treated with corticosteroids or immunosuppressants; the remaining patient died of multiple organ failures. Nine patients switched to alternate TNF- $\alpha$ inhibitor: vasculitis reoccurred in 1. TNF- $\alpha$ inhibitor was continued in 6; all experienced resolution.	Agent discontinued in 33 patients; 18 resolved without further treatment, 14 were treated with corticosteroids or immunosuppressants; the remaining patient died of multiple organ failures. Nine patients switched to alternate TNF- $\alpha$ inhibitor: vasculitis reoccurred in 1. TNF- $\alpha$ inhibitor was continued in 6; all experienced resolution.

A = adalimumab; AS = ankylosis spondylitis; E = etanercept; I = infliximab; JIA = juvenile idiopathic arthritis; PsA = psoriatic arthritis; RA = rheumatoid arthritis; TNF- $\alpha$  = tumor necrosis factor- $\alpha$ .



**Figure 3.** Leukocytoclastic vasculitis, palpable purpura that developed in a patient with Crohn's disease who was receiving infliximab infusions. This patient developed mild lower-extremity cutaneous leukocytoclastic vasculitis that was not accompanied by systemic symptoms. The purpura resolved after infliximab therapy was discontinued.

papulosquamous or butterfly rash ( $p = .011$ ). Development of ANAs has not yet been seen to give rise to side effects or to impede the efficacy of treatment.

### Psoriasiform Skin Lesions

Infliximab and etanercept have been approved for the treatment of psoriasis and are generally highly efficacious drugs for this condition. It is therefore of the utmost interest that a number of reports of TNF- $\alpha$ -inhibitor-



**Figure 4.** Cutaneous lupus erythematosus. Infiltrated erythematous plaques developed on the face and chest of a female patient with psoriasis who was being treated with etanercept. Skin biopsy specimens revealed interface dermatitis and a superficial and deep lymphocytic infiltrate. The patient also exhibited positive antinuclear antibody and anti-double-stranded deoxyribonucleic acid (anti-dsDNA) antibodies.

induced psoriasiform lesions have surfaced in postmarketing observations. One large review of 120 cases<sup>43</sup> and 3 smaller reports give some indication as to the rate of induced psoriasiform lesions: the overall rates appear to be between 1.0% and 5.3%.<sup>44–47</sup> Summaries of these reports are available in Table 5.

In general, patients are able to tolerate the new-onset psoriasis without discontinuation of the TNF- $\alpha$  inhibitor in favor of the benefit it provides to their primary disease process.<sup>44–56</sup> The locations of the lesions varied, but there was a strong predilection to develop lesions on the palms and soles, even in the absence of diagnosed palmoplantar pustulosis (PPP) (Fig 5). Other common sites were the limbs (particularly the pretibial area) and the torso (Fig 6). Involvement of the scalp and behind the ears was seen, but less so than were other presentations.

The pathophysiology of how TNF- $\alpha$  inhibitors might cause these psoriasiform lesions is not understood. One proposal by de Gannes and colleagues<sup>57</sup> is that there is a cross-regulation between TNF- $\alpha$  and interferon (IFN)- $\alpha$ , which may lead to an increase in IFN, resulting in psoriatic lesions. The investigators looked at the biopsy specimens of 15 patients undergoing TNF- $\alpha$  inhibitor therapy with new onsets or exacerbations of psoriasis and found increased levels of myxovirus-resistance protein A, a surrogate marker for type I IFN activity.

TNF- $\alpha$ -induced psoriatic lesions have also been hypothesized to share a common mechanism to other TNF- $\alpha$ -inhibitor-induced autoreactive processes. As previously stated, these drugs have a well-known side effect of inducing ANA formation and the occasional manifestation of autoimmune syndromes. It is possible that the drugs may induce the activation of autoreactive T cells that in turn lead to psoriatic lesions.<sup>58</sup> Another possibility, which may act independently or complement the prior theory, is that of an up-regulation of chemokine receptors, specifically CXCR3, which increases cutaneous trafficking of autoreactive T cells. Aeberli and colleagues found that treatment of RA patients with infliximab and etanercept resulted in increased numbers of peripheral T cells expressing CXCR3.<sup>59</sup> An alternative mechanism has been proposed for the PPP variant. It has been suggested that the pathogenesis of PPP may be due to a relative impairment of neutrophils induced by the TNF- $\alpha$  inhibitor, which subsequently would allow the growth of *Propionibacterium acnes*, which is implicated in the pathogenesis of this disease.<sup>60</sup> Another possibility relates specifically to the dysfunction of palmar eccrine sweat glands, related to TNF- $\alpha$  blockade.<sup>61</sup>

**Table 4.** Studies Reporting Incidence of Drug-Induced Lupus Erythematosus with Tumor Necrosis Factor- $\alpha$  Inhibitors

Study Type	Diseases Being Treated			TNF- $\alpha$ Inhibitor Implicated	Demographics	Symptoms	Laboratory Findings	Treatment Given
	Cases							
Medline search identifying 53 cases of reported TNF- $\alpha$ inhibitor-induced lupus erythematosus <sup>39</sup>	33 cases (20 were rejected based on only cutaneous findings or presence of mixed connective-tissue disease)	RA (25)	I (21)	None available	Rash NOS (73%), polysynovitis (52%), fever (52%), myalgias (24%), pericardial or pleural effusion (18%), nephritis (9%)	Positive ANA in 100%, dsDNA in 91%, hypocomplementemia in 59%, antihistone antibody in 57%	Not available	
		JIA (3)	E (10)					
Review of literature of 1990–2006 investigating autoimmune diseases associated with TNF- $\alpha$ inhibitor therapy <sup>25</sup>	92	PsA (2)	A (2)	Average age at time of onset: 50.9 years Average length of treatment with TNF- $\alpha$ inhibitor: 41.2 weeks	Cutaneous features (67%), arthritis (31%), serositis (12%), nephropathy (7%), oral ulcers (4%), CNS involvement (3%)	Elevated ANA in 79%, dsDNA in 72%, cytopenia in 22%, antiphospholipid antibodies in 11%, anti-Smith antibodies in 10%	Corticosteroids in 40%; other immunosuppressants in 12% TNF- $\alpha$ inhibitor discontinued in 94%	
		CD (2)						
		AS (1)						
		Mixed connective-tissue disease (2)						
		JIA (1)						
Authors' review of published reports of cutaneous lupus not reviewed in Costa et al article <sup>31–38</sup>	17	RA (17)	I (9)	Average time to onset: 10.4 months (14 patients)	Pruritic rash (3), butterfly distribution (3), photo distribution (3), erythematous plaques (4), purpura (2), chilblains (1), rash NOS (1)	ANA titers > 1:40 in all patients, dsDNA in 88%; reporting of other autoantibodies inconsistent	TNF- $\alpha$ inhibitor discontinued in 5/7 cases (not reported in others); skin lesions and other symptoms resolved in 6/7 cases	
			E (7) A (1)					

A = adalimumab; ANA = antinuclear antibody; AS = ankylosing spondylitis; CD = Crohn's disease; CNS = central nervous system; dsDNA = double-stranded deoxyribonucleic acid; E = etanercept; I = infliximab; JIA = juvenile idiopathic arthritis; NOS = not specified; PsA = psoriatic arthritis; RA = rheumatoid arthritis; TNF- $\alpha$  = tumor necrosis factor- $\alpha$ .

**Table 5.** Reports of Psoriatic Lesions Induced by Tumor Necrosis Factor- $\alpha$  Inhibitors

<i>Study Type or Description</i>	<i>Cases</i>	<i>Disease Being Treated</i>	<i>TNF-<math>\alpha</math> Inhibitor</i>	<i>Demographic Information</i>	<i>Manifestation of Psoriasisiform Lesion</i>	<i>Personal or Family History</i>	<i>Resolution</i>
Prospective study of 150 patients receiving TNF- $\alpha$ inhibitors (looking for new cutaneous disease) <sup>45</sup>	8	RA (4) AS (3)	I (3) E (3) A (2)	4 men, 4 women Average time to onset: 6.6 months (range, 2 weeks to 17 months)	Psoriasis vulgaris (5), palmoplantar pustular psoriasis (3)	Two cases were exacerbations of pre-existing psoriatic conditions	—
Review of published case reports of TNF- $\alpha$ inhibitor-induced psoriasis, with 6 cases introduced by authors <sup>43</sup>	120 reviewed, 6 original	RA (61) AS (21) PsO and PsA (12 total) Inflammatory bowel disease (10)	I (63) E (37) A (26)	72 women, 36 men Average age: 42.3 years Time to onset of lesions: 7.0 mo for etanercept, 9.8 mo for infliximab, 12.5 mo for adalimumab (no statistical significance)	Psoriasis (73), palmoplantar pustular psoriasis with or without psoriatic lesions (37), psoriatic drug eruption (10)	25 patients had personal history of psoriasis; 8 had family history (family history available only in 74 cases)	Discontinued in 47, with complete resolution in 21, partial in 20, no response in 3 (remaining 3 not reported) Continued treatment of psoriasis in 47, with complete response in 22, partial in 35, and stable disease in 2; switching TNF- $\alpha$ inhibitors in 6 patients resulted in improvement in 5
Case series <sup>46</sup>	6 cases in 400 patients treated with TNF- $\alpha$ inhibitors	RA CD Other spondyloarthropathies AS	I (3) E(1) I and E (2)	5 women, 1 man Average age at onset: 52.1 years Average time to onset: 13.8 months' treatment (range, 1.5 days to 4 years)	Psoriasis (3), PPP (3)	No personal or family history of psoriasis	Continued in 4 cases, stopped in 2; all cases were treated symptomatically with complete or near complete resolution
Case series <sup>47</sup>	2 patients of 166 treated	RA (2)	I (2)	2 women Average age: 37 years Average to time of onset: 18.5 months	PPP (2)	No personal or family history of psoriasis	Both patients switched to another TNF- $\alpha$ inhibitor; 1 patient resolved

A = adalimumab; AS = ankylosing spondylitis; CD = Crohn's disease; E = etanercept; I = infliximab; PPP = palmoplantar pustulosis; PsA = psoriatic arthritis; PsO = psoriasis; RA = rheumatoid arthritis; TNF- $\alpha$  = tumor necrosis factor- $\alpha$ .





**Figure 5.** Palmar pustulosis occurring in a patient with rheumatoid arthritis who was being treated with etanercept.

### Rebound Phenomenon in Psoriasis

The most notorious cutaneous effect connected to efalizumab is a rebound phenomenon. This is defined as a relapse of psoriasis that is worse than the original disease ( $> 125\%$  of the baseline global severity score or psoriasis area-severity index [PASI] score). The results of four clinical trials are reported in Table 6. Although rebound or changing presentation of psoriasis while on efalizumab has been reported,<sup>62,63</sup> not all trials reflect this finding.<sup>19,64</sup>

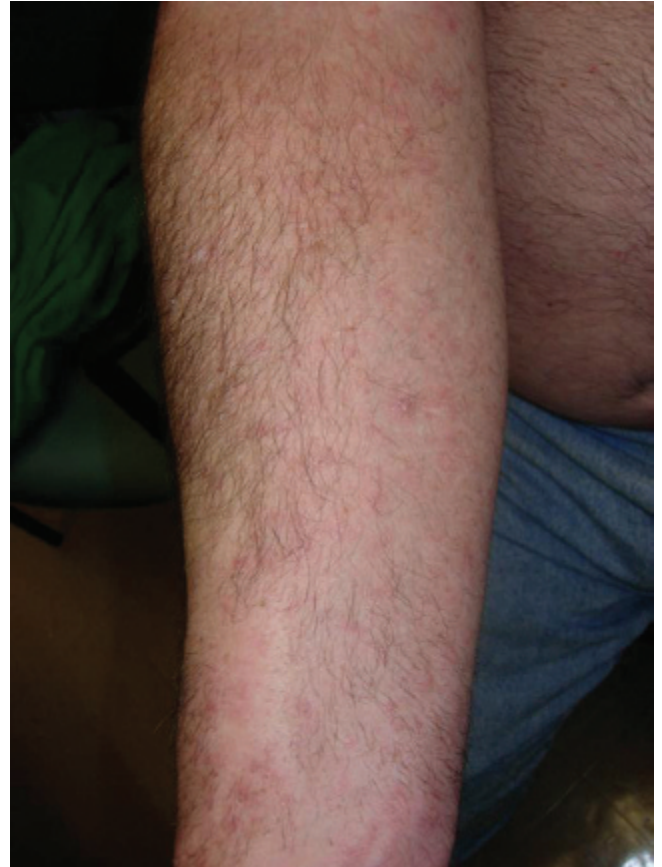
Menter and colleagues recently published a study regarding the frequency of rebound with efalizumab and the transitioning of patients to other immunosuppressants.<sup>65</sup> Of their 130 patients who received efalizumab (1 mg/kg per week for 12 weeks), rebound was not observed in those who were PASI-75 responders ( $n = 46$ ) but was observed at a significant rate in nonresponders (14 of 49). Rebound was not observed in the 8 patients treated with cyclosporine and was observed in only 2 of 12 patients treated with methotrexate during the transition period. However, breakthrough of psoriatic rebound has been reported even while patients are on cyclosporine.<sup>66</sup>

### Eczema

There is evidence that TNF- $\alpha$  inhibitors can lead to eczema (Table 7); however, there exists the possibility of significant underreporting with this condition. One study of 142 RA patients found that 47% of the participants had some eczema-like symptoms.<sup>67</sup>

### Atopic Dermatitis

The interaction between the TNF- $\alpha$  inhibitors and atopic dermatitis (AD) is a particularly interesting one. There



**Figure 6.** Guttate psoriasis flare during anti-tumor necrosis factor- $\alpha$  therapy. This patient was a 44-year-old male with plaque psoriasis who was being treated with etanercept. After his third month of therapy, he developed guttate lesions on his trunk and extremities. Narrowband ultraviolet B was used to treat this, with a good outcome.

have been a number of case reports of AD as a side effect of TNF- $\alpha$  inhibitors, as well as a proposal for these drugs to be used as a treatment for AD. For published cases, see Table 7.

Although off-label use of TNF- $\alpha$  inhibitors for AD has found limited appeal, there has been some success in its use. Jacobi and colleagues tested infliximab in the treatment of AD in 9 patients; two of them had maintained an excellent response by 46 weeks after completion of therapy.<sup>68</sup>

### Erythema Multiforme, Stevens-Johnson Syndrome, and Toxic Epidermal Necrolysis

TNF- $\alpha$  itself is thought to play an important role in the manifesting of erythema multiforme, yet there are cases in which the inhibitors of TNF- $\alpha$  have precipitated it (see Table 7).

**Table 6.** Rebound Psoriasis or Change in Psoriatic Patterns with Efalizumab

<i>Description of Study</i>	<i>Cases</i>	<i>Incidence of "Rebound" Psoriasis</i>
Combined placebo-controlled clinical trials of efalizumab (1 mg/kg/wk for psoriasis for 12 weeks) <sup>62</sup>	1,620 treated, 715 controls	Adverse psoriatic events, including pustular, erythrodermic and guttate subtypes in 3.2% of treatment patients, 1.4% of controls; 0.7% of treated patients were said to have worsening of disease during treatment or after discontinuation.
Placebo-controlled clinical trial of efalizumab (1 mg/kg/wk for psoriasis for 12 weeks) <sup>63</sup>	421 treated, 218 controls	2.2% of treatment patients manifesting psoriasis-related adverse events vs 0.8% of controls; included guttate and erythrodermic changes.
Placebo-controlled clinical trial of efalizumab (1 mg/kg/wk for psoriasis for 12 weeks) <sup>64</sup>	529 treated, 264 controls	Psoriatic adverse events were reported in 13.6% of treatment patients and 11.2% of placebo patients; however, these statistics included pruritus. Erythroderma events occurred in 1.7% of treatment patients and 0.4% of placebo patients.
Placebo-controlled clinical trial of efalizumab (1 mg/kg/wk for psoriasis for 12 weeks, with re-treatment extending to 24 weeks) <sup>19</sup>	328 treated, 170 controls	Psoriatic adverse events were recorded in weeks 13–24: 16.9% in placebo group, 5.3% in 1-mg/kg group, and 3.0% in 2-mg/kg group.

There has been one case report of Stevens-Johnson syndrome associated with rituximab.<sup>69</sup> The patient was a 33-year-old male being treated for non-Hodgkin's follicular lymphoma. During the second infusion of rituximab at 375 mg/m<sup>2</sup>, grade 1 mucositis was noted. The patient received the third infusion on schedule despite weight loss and a pruritic trunk rash. After the diagnosis of Stevens-Johnson syndrome was made, rituximab was discontinued, and the patient was treated with acyclovir, fluconazole antibiotics, antiseptic cream, and potassium permanganate bath solution. The syndrome persisted for over a year until his death.

The only other cases of note are two cases of toxic epidermal necrolysis (TEN) in two rhesus macaques.<sup>70</sup> There have been no reports of TEN in humans with the administration of rituximab or any of the other biologics we reviewed.

### Urticaria

Of the TNF- $\alpha$  inhibitors, infliximab was the only one for which urticaria was reported as a significant side effect. Among RA patients ( $n = 688$ , 6% of those in the treatment group (3–10 mg/kg) developed urticaria as opposed to 1% of those on placebo. In CD patients ( $n = 255$ ), 3% of those

**Table 7.** Other Inflammatory and Allergic Conditions Associated with TNF- $\alpha$  Blockade

<i>Proposed Cutaneous Side Effect</i>	<i>Articles Reporting Side Effects</i>	<i>Number of Cases</i>	<i>TNF-<math>\alpha</math> Inhibitor Implicated</i>	<i>Disease Being Treated</i>	<i>Discontinuation and Rechallenge</i>	<i>Notes</i>
Eczema	Prospective study of 289 patients, <sup>44</sup> case report <sup>87</sup>	20*	I (1)	RA (289) CD (1)	Discontinued in 4 patients; 1 patient rechallenged with recurrence	Types included dyshidrotic (5), contact (4), nummular (1), papular (1), and nonspecific (8).
Atopic dermatitis	Case reports <sup>45,88–90</sup>	7	I (6) E (1)	RA (2) PsO (2) JIA (1) CD (1) AS (1)	Resolved only in 1 patient who discontinued (Lee, <sup>45</sup> not listed)	Average time to onset: 6 weeks. Two patients had history of atopic dermatitis.
Erythema multiforme	Case reports <sup>91–93</sup>	5	I (3) E (1) A (1)	RA (5)	Discontinued in all 5 cases; all resolved	Topical and oral corticosteroids were used in aid of resolution.

A = adalimumab; AS = ankylosing spondylitis; CD = Crohn's disease; E = etanercept; I = infliximab; JIA = juvenile idiopathic arthritis; PsO = psoriasis; RA = rheumatoid arthritis.

\*6.6% of patients in the study by Flendrie et al.<sup>44</sup>

in treatment (3–10 mg/kg) developed urticaria, versus none of those on placebo.<sup>1</sup>

Urticaria is a common side effect of rituximab; incidence in nonrandomized trials ranged from 3 to 14%.<sup>71–73</sup> However, two other studies treating B-cell malignancy in 108 patients made no report of any incidents of urticaria.<sup>74,75</sup> Unfortunately, no double-blind studies indicate rates of urticaria in treatment of malignancy versus rates for placebo.<sup>76</sup>

Of interest, the rate of urticaria may be lower when rituximab is used in the treatment of RA. In a placebo-controlled randomized study of 520 patients being treated for RA with two infusions of rituximab (1 g) plus methotrexate, Cohen and colleagues reported urticaria in only 2% of treatment patients for the first infusion and no urticaria for the second.<sup>77</sup> This was not a statistically significant difference from the placebo results.

An unusual pattern of the urticaria associated with rituximab has been observed. One report described a 37-year-old man who developed urticaria 1 hour after an initial infusion at the site of tumor patches and excision scars.<sup>78</sup> The man did not develop any urticaria on later infusions as seems to be a frequent pattern with the use of this drug. A similar reaction was described as occurring in one subject in a study of 10 patients being treated for cutaneous B-cell lymphoma.<sup>79</sup> The authors hypothesized that the reaction in this case was due to the killing of CD20-positive B cells, which led to cytokine release at the site of the tumor, leading to a local urticarial reaction.

Generally, the development of urticaria can be minimized by slowing the infusion rate of rituximab or by pretreating with antihistamines. Pretreatment with antihistamines is in fact so common that the true frequency of urticarial side effects may be underestimated.<sup>78</sup>

## Conclusion

Although infusion reactions (IRs) appear to be fairly common with infliximab, trials do not currently indicate usefulness of pretreatment for the prevention of IRs; rather, maintaining a regular dosing schedule appears to be the best way to prevent immunologically mediated complications. Injection site reactions are an issue with etanercept, adalimumab, and alefacept although this can often be managed by varying the site of injection. The relationship between vasculitis and TNF- $\alpha$  inhibitors remains unclear although the two large available studies do not reveal resolution of symptoms with discontinuation

of the possibly offending drug, making this relationship suspect. Current literature indicates that both etanercept and the TNF- $\alpha$  inhibitors in general may have an increased rate of cutaneous manifestation of drug-induced lupus when compared with other kinds of drug-induced lupus. The rates of development of new psoriasiform lesions with the TNF- $\alpha$  inhibitors appears to be between 1.0% and 5.3%, although patients are generally able to continue the medication in favor of the treatment it provides for their primary disease process. Urticaria appears to be an issue with infliximab and rituximab alone of the biologics reviewed, and this issue appears to typically be controllable by pretreatment with antihistamines.

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