

A Mechanism-Based Classification of Dermatologic Reactions to Biologic Agents Used in the Treatment of Cutaneous Disease: Part 1

Matthew Bremmer, April Deng, and Anthony A. Gaspari

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- α inhibitors, have a number of varied dermatologic side effects. In this two-part article, we perform a review of literature regarding the cutaneous side effects of infliximab, etanercept, adalimumab, rituximab, efalizumab, and alefacept. In Part 1, we will discuss cutaneous infections, malignancy, rebound phenomenon, eczema, atopic dermatitis, lichenoid reactions, granulomatous disease, pruritus, acne, and progressive multifocal leukoencephalopathy.

BIOLOGIC THERAPIES have been in use for over a decade now. Infliximab and etanercept were first approved in 1998 for treatment of rheumatoid arthritis (RA) and Crohn's disease (CD), respectively.¹ Shortly thereafter, adalimumab was added to the armament of tumor necrosis factor- α (TNF- α) inhibitors. These medications bind soluble TNF- α and, to some degree, receptor-bound TNF- α as well.²⁻⁴ All of these drugs have good efficacy in reducing the symptoms of a number of autoimmune diseases.^{2,5,6}

Although they are typically tolerable, the drugs can have some significant side effects, which lead to discontinuation. Among these side effects are a number of potential cutaneous side effects that have been reported. A prospective study done in 2005 that followed 289 patients who were receiving TNF- α -blocking therapy for RA revealed that 25% of the patients receiving therapy sought the attention of a dermatologist while receiving therapy, compared with 13% of controls ($p < .0005$).⁷ A prospective study of 150 patients with rheumatic diseases who were using TNF- α antagonists found that 35 (23%) of

the 150 patients developed some sort of new dermatologic condition while on therapy.⁸

Other biologic agents used by dermatologists have likewise been reported to have cutaneous side effects. Rituximab is a chimeric monoclonal antibody that binds with a high degree of specificity to the antigen CD20 found on mature B and pre-B lymphocytes. This drug was primarily developed (and is currently licensed) for the treatment of CD20-positive non-Hodgkin's lymphoma. In addition to this use, rituximab has been used to treat a variety of dermatologic conditions, including dermatomyositis⁹ and pemphigus foliaceus.¹⁰ Although generally a well-tolerated drug, it has been associated with a number of cutaneous side effects, including urticaria and Stevens-Johnson syndrome.¹¹

Finally, efalizumab and alefacept are two Food and Drug Administration (FDA)-approved biologics currently being marketed for use for psoriasis. Alefacept is a fusion protein of human leukocyte-function-associated antigen 3 (LFA-3) and the Fragment Constant (Fc) portion of human immunoglobulin G1 (IgG1), which binds to surface CD2 T cells.¹² Efalizumab has a distinctly different mechanism of action; it is a monoclonal antibody that binds to human CD11a and serves to block the activation of lymphocytes as well as their migration and adhesion to keratinocytes.¹³ Both of these drugs have been associated with various cutaneous side effects.

We reviewed the literature, using PubMed to find publications that reported cutaneous side effects during the use of infliximab, etanercept, adalimumab, rituximab, efalizumab, and alefacept, and summarized the prevalence

From the Department of Dermatology, University of Maryland, Baltimore, MD.

Address reprint requests to Anthony A. Gaspari, MD, Albert Shapiro Professor and Chairman of Dermatology, University of Maryland, 405 West Redwood Street, 6th Floor, Baltimore, MD 21201-1734. E-mail: agasp001@umaryland.edu

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of any suspected induced dermatologic conditions associated with these medications. In this article, we discuss cutaneous infections, malignancy, rebound phenomenon, eczema, atopic dermatitis, lichenoid reactions, granulomatous disease, pruritus, and acne.

Infections

Perhaps the most important concern regarding use of TNF- α inhibitors has been the possibility of increased rates of infection. While initial clinical trials did not indicate an increased rate of infection, postmarketing data have shown an increased number of infections among users of TNF- α inhibitors. Tuberculosis in particular has been associated with these drugs, most strongly with infliximab.^{14–16}

Figure 1 is an example of osteomyelitis of the great toe from saureus that occurred in a psoriasis patient treated with infliximab. Figure 2 represents HSV in the setting of a patient treated with infliximab. A variety of both systemic and cutaneous infections have been linked to TNF- α blockade, including bacterial, viral, and fungal infections. These studies are summarized in Table 1. Although they all showed noteworthy rates of infection, none of these studies were placebo controlled. Larger studies, however, do not make specific note of rates of cutaneous infection; they tend to simply note statistics on infections as a whole (Table 2). Of note, one placebo-controlled trial of etanercept for treatment of psoriasis in 211 children found that warts occurred in 16 children who were treated with etanercept, whereas none occurred in those given placebo.¹⁷

Numerous case reports have been published regarding cutaneous infections with the use of TNF- α inhibitors



Figure 1. Infliximab induced osteomyelitis of the right toe. The patient had severe psoriasis and was responding well to infliximab therapy. The patient also had type 2 diabetes and developed an ulcer on the toe that developed osteomyelitis.

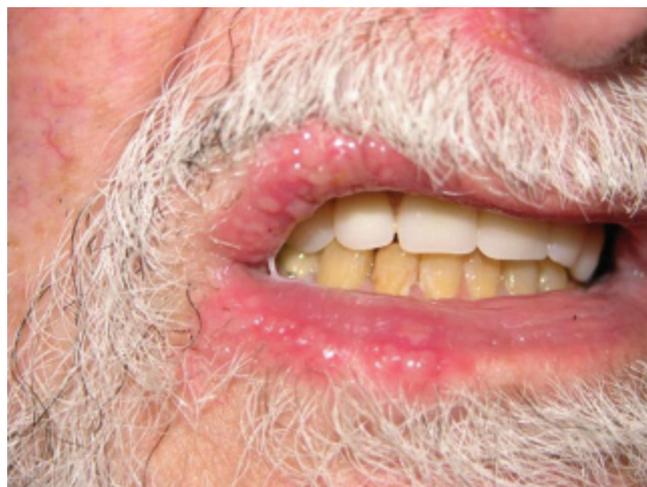


Figure 2. HSV in a patient on infliximab infusions for severe psoriatic arthritis. The patient had been treated with infliximab for many years without complications. The HSV occurred after the patient experienced a flu-like illness.

(Table 3). Although these tell us little about the rates of infection, reports of infections such as those with *Nocardia* indicate that infections usually found in the immunosuppressed can be found in patients who are using these medications.

Although the reporting of infections commonly found in immunocompromised hosts is concerning, it has yet to be firmly established that the use of TNF- α inhibitors leads to an actual increase in the rates of infection (see Table 2). A study by Dixon and colleagues examined 7,664 patients with RA treated with anti-TNF- α antibodies versus 1,354 controls treated with disease-modifying antirheumatic drugs (DMARDs) found an increased incidence of skin and soft-tissue infections with an adjusted increase in relative risk (IRR) of 4.28 (95% confidence interval, 1.06–17.17).¹⁸

While understanding the implications of TNF- α inhibitor therapy on the immune system has proven difficult enough, a number of confounding variables exist, including the disease being treated and other immunomodifying drugs the patient may be taking. Patients with RA have an increased rate of infection compared to the general population (19.64 infections per 100 person-years in the RA population vs 12.87 infections per 100 person-years in the general population).¹⁹ Many of the patients studied were simultaneously or previously taking methotrexate, which also increases the risk of infection.²⁰ More study will be required to understand the role of TNF- α inhibitors in cutaneous infection.

Additionally, there is evidence of increased rates of infection with rituximab, although specific evidence of cutaneous infection is less conclusive. In a placebo-

Table 1. Summary of Studies of Infections with Tumor Necrosis Factor- α Inhibitors

Study	Type of Study	No. of patients; No. of Patients with Infection	Time from Initiation of Therapy to Event	TNF- α Used	Infections
Lee HH et al ⁸	Prospective study of cutaneous side effects of TNF- α inhibitors for treatment of rheumatic disease	150; 13 developed cutaneous infections	7.6 months (mean)	Infliximab (8) Adalimumab (4) Etanercept (1)	Pityriasis versicolor (3), tinea corporis (3), microbial eczema (5), herpes simplex (1), <i>Staphylococcus aureus</i> (1)
Flendrie M et al ⁷	Prospective study of patients treated with TNF- α inhibitors for RA	289; 27 developed 33 cutaneous infections	9.1 months (median)	Adalimumab (14) Infliximab (12) Etanercept (6) Lenercept (1)	Fungal (20), bacterial (11), viral (2)
Colombel JF et al ⁶⁷	Retrospective study of 500 patients receiving infliximab for CD	500; 48 infections (10 cutaneous)	2.4 infusions	Infliximab	Cellulitis (3), shingles (2), chicken pox (1), genital herpes (1), onychomycosis from <i>Candida</i> (1), infected scar from <i>Serratia marcescens</i> (1), perioral infection from <i>Haemophilus bicans</i> (1)

CD = Crohn's disease; RA = rheumatoid arthritis; TNF = tumor necrosis factor.

controlled study of 465 patients being treated for refractory RA with rituximab 500 mg or 1000 mg for two doses 15 days apart (patients all additionally received methotrexate, and many also received intravenous and/or oral glucocorticoids), infection occurred in 35% of the rituximab group and 28% of the placebo group (statistical significance was not calculated). Cutaneous infections were not noted.²¹ In the trial of rituximab for RA conducted by Cohen and colleagues, infection rates were 38% in the placebo group and 41% in the rituximab-treated group,²² again without note of cutaneous infection.

As for rates of infection in patients being treated for B-cell non-Hodgkin's lymphoma, in a phase III open-label trial of rituximab (375 mg/m² weekly for 4 weeks in 166 patients), 30% of patients experienced an infectious event. Only two patients were reported to have cutaneous infections; these were a case of herpes simplex infection and a case of ophthalmic herpes zoster.²³ In a phase II study of 75 patients in which rituximab (375 mg/m²) was given for as long as a year, 7 opportunistic infections were reported, including 3 cases of dermatomal herpes zoster (baseline rate in the population, 3.6 per 1,000 person-years)²⁴ and 4 cases of localized herpes simplex.²⁵ Other trials of rituximab for non-Hodgkin's lymphoma made no report of infections in a total of 69 patients.^{26,27}

There is some evidence of an increased incidence of herpes simplex with the use of efalizumab. A study of 686

patients for 12 weeks by Papp and colleagues revealed an incidence of labial or oral herpes of 3.1% in treated patients versus 0.8% in the placebo group.²⁸ Similar results were found in the 793-patient study by Dubertret and colleagues, who found a 3.1% rate of herpes in the treatment group versus a 1.9% rate in the placebo group.²⁹ The only other incidence of increased rates of infection found in clinical trials was in a 12-week multicenter randomized controlled trial of 556 patients with psoriasis, in which there was a greater than 1% increase in the rates of impetigo and cellulitis for those receiving efalizumab (1 mg/kg) when compared to those taking placebo.³⁰

Cutaneous Neoplasms

Establishing the relationship between TNF- α inhibition and malignancy is not easy. The development of malignancy is generally a long-term event. Furthermore, rates of malignancy are increased in patients suffering from diseases frequently treated by TNF- α inhibitors, including RA³¹ and psoriasis.³² Two cutaneous malignancies whose relation to TNF- α inhibitors is debated are squamous cell carcinoma (SCC) and T-cell lymphoma.

Currently, there are limited studies on the incidence of squamous cell carcinoma related to TNF- α inhibition. A study by Lebwohl and colleagues published in 2005 found no increased risk of SCC in patients who were taking

Table 2. Rates of Generalized Infections in Tumor Necrosis Factor- α Inhibitors

<i>Placebo-Controlled Trials</i>	<i>Rates of Infection</i>
Etanercept: 618 patients treated for psoriasis randomized to receive 50 mg twice weekly for 12 weeks, or placebo ⁶⁸	Placebo: 23.2% Etanercept: 27.9% Only one serious infection (which was in the placebo group) reported
Etanercept: 591 patients treated for psoriasis randomized to receive twice weekly for 12 weeks, or placebo. After 12 weeks, all patients received 50 mg etanercept ³⁷	Placebo: 130.5/100 patient-years Etanercept: 103.9/100 patient-years
Etanercept: 211 children aged 4–17 years with psoriasis randomized to 0.8 mg/kg once weekly for 12 weeks or placebo; all then received treatment for 24 weeks, then were rerandomized to placebo for 12 weeks ¹⁷	Placebo: 308.3/100 patient-years Etanercept: 229.3/100 patient-years
Adalimumab: 854 patients treated for CD with placebo, 40 mg adalimumab every other week, or 40 mg weekly, after all patients received induction treatment with adalimumab, two doses (80 mg, 40 mg, 2 weeks later) ⁶⁹	Placebo: 36.8% 40 mg every other week: 46.2% 40 mg weekly: 44.4%
Infliximab and adalimumab multistudy analysis of 5,014 patients treated for RA with drug or placebo ⁷⁰	Increase in relative risk for serious infections; relative risk, 3.0 (95% CI, 1.8–5.1)
Infliximab, etanercept, and adalimumab: prospective observational study of 7,664 patients treated for RA with anti-TNF- α antibodies versus 1,354 DMARD-treated controls ¹⁸	Rate of serious infections not increased; incidence rate ratio, 1.03 (95% CI, 0.68–1.57) Incidence of skin and soft-tissue infections increased; adjusted IRR, 4.28 (95% CI, 1.06–17.17)
Infliximab, etanercept, and adalimumab analysis of 4,167 patients treated for RA in Sweden with TNF- α inhibitors, cross-referenced with all patients with RA who were hospitalized and with all patients hospitalized with infection between 1999 and 2003 ⁷¹ ; analysis for increased rates of hospitalization due to infection in TNF- α inhibitor users	Risk ratio versus control RA patients, 1.43 (95% CI, 1.18–1.73) in first year of treatment, but no subsequent increase in rates of infection for the subsequent 2 years
Infliximab, etanercept, and anakinra: retrospective analysis of 858 patients treated for RA with TNF- α inhibitors (346 infliximab, 512 etanercept) from German database analyzing for increased rates of serious and nonserious infections ⁷²	Rates of skin and subcutaneous tissue infection per 100 patient-years was found to be elevated: 6 in etanercept, 7.68 in infliximab, 2.63 in controls ($p = .0017$)
Analysis of postmarketing data on adalimumab in patients treated for RA; 10,050 patients were included in the analysis, which includes all patients in database until April 2005; one point of analysis was rates of infection ⁷³	Rate of serious infection was 5.1/100 patient-years (less than in published reports of infections in RA patients at baseline) ¹⁹

CD = Crohn's disease; DMARD = disease-modifying antirheumatic drug; IRR = increase in relative risk; RA = rheumatoid arthritis; TNF = tumor necrosis factor.

etanercept.³³ They studied 1,442 patients with RA from the clinical trials database and cases reported to the post-marketing database on the 125,000 patients who had taken etanercept at the time. It was found that only 4 cases of SCC were reported in clinical trials (2.8 cases per 1,000 patients), in a total of 4,257 years of patient exposure (0.9 SCC per 1,000 patient-years), which compared favorably with the baseline SCC rate of 13.1 for Arizona and 5.9 for Minnesota.^{34,35} Additionally, the study noted that the rate of postmarketing reporting indicated 1 incident per 10,000 patient-years, although this is almost certainly affected by

underreporting. Not all trials of TNF- α inhibitors have made note of the rates of nonmelanoma skin cancers (NMSCs), but among those that have, rates of these malignancies have not been elevated.^{36,37}

In contrast, a report published the same year by Chakravarty and colleagues³¹ indicated some correlation between NMSCs and TNF- α inhibitors. A total of 15,789 patients with RA and 3,639 patients with osteoarthritis were studied via a self-reporting system, in search of differences between the rates of NMSCs in the two groups. The rate of NMSCs in RA patients was 18.1 cases per 1,000

Table 3. Noteworthy Case Reports of Cutaneous Infections with Tumor Necrosis Factor- α inhibitors

<i>Infection</i>	<i>TNF-α Inhibitor</i>	<i>Duration of Prior Treatment</i>	<i>Disease Being Treated</i>	<i>Associated Medication</i>
<i>Nocardia</i> ⁷⁴	Infliximab	3 infusions	CD	Prednisone
<i>Nocardia</i> ⁷⁵	Infliximab	9 infusions	RA	Azathioprine
Necrotizing fasciitis ⁷⁶	Infliximab	NA	RA	Methotrexate
Necrotizing fasciitis ⁷⁷	Etanercept	7 months	RA	Prednisone
Bacterial infection of ulceration developing into osteomyelitis (see Figure 1) ⁷⁸	Infliximab	6 months	PsA	NA
Varicella zoster ⁷⁹	Infliximab	3 infusions	CD	NA
Herpes simplex ⁸⁰	Infliximab	14 months	RA	Methotrexate
Molluscum contagiosum ⁸¹	Infliximab	6 months	RA	Methotrexate
<i>Cryptococcus</i> ⁸²	Adalimumab	NA	RA	Methotrexate, hydroxychloroquine

CD = Crohn's disease; NA = not applicable; PsA = psoriatic arthritis; RA = rheumatoid arthritis; TNF = tumor necrosis factor.

patient-years for all comers, regardless of TNF- α inhibitor use. However, within the group of RA patients, the researchers found a possible (though not statistically significant) correlation between the use of TNF- α inhibitors and NMSCs ($p = .089$) and a definite correlation when TNF- α inhibitors were used concomitantly with methotrexate ($p = .001$).

Although larger studies are required to detect a subtle increase in malignancy, there are a few case reports worthy of note. There have been published reports of patients' developing multiple squamous cell carcinomas both after treatment with infliximab³⁸ and treatment with etanercept,³⁹ without concomitant immunosuppressant use. In the latter case, the lesions regressed after discontinuation of the etanercept. Another patient developed an extremely rare SCC of the penis 3.5 months after starting on etanercept therapy.⁴⁰ It has been proposed that the inhibition of Th1 cytotoxic response by TNF- α blockade impedes the ability of the body's immune surveillance to suppress malignancy.⁴¹

Cutaneous T-cell lymphoma is a very rare disease, having a baseline incidence of 0.6 cases per 100,000 population per year.⁴² With such a low incidence, establishment of a correlation with TNF- α inhibitors has not been studied. Although there have been a number of reports of patients' manifesting cutaneous T-cell lymphoma while using TNF- α inhibitors,^{7,43,44} there is no convincing evidence that TNF- α inhibitors are connected to this condition.

Immunosuppressive therapy is associated with the development of eruptive benign melanocytic nevi.⁴⁵ Although no strong association has been made between TNF- α inhibitors and the development of nevi, reports of

three cases of patients' developing new nevi while on TNF- α inhibitor therapy have been published.^{46,47} Recently, two case reports of metastatic melanoma after the initiation of TNF- α inhibitor therapy have been published⁴⁸; the two patients developed metastatic melanoma 6 and 8 years, respectively, after having the primary lesions removed. More cases would be needed to create a clear connection between this condition and TNF- α inhibitors.

Only one clinical trial, an open-label extension trial of 1,039 patients treated for RA, made note of new malignancies occurring during treatment with rituximab.⁴⁹ Twenty-six new malignancies were noted in this trial, including 6 basal cell carcinomas, 2 SCCs, 2 malignant melanomas, 3 breast malignancies, and no new lymphomas. This trial had no placebo arm for comparison. Other large trials have not reported incidences of malignancy.^{21,22,25,26} There have been two published reports regarding a recurrent squamous cell carcinoma and a Merkel cell carcinoma in patients who had been given rituximab, but neither report showed convincing evidence for or against involvement of the drug.^{23,50} The current evidence gives no evidence for or against increased incidence of malignancy associated with rituximab.

There is also some evidence of malignancy with alefacept. Clinical trials found that, among 1,357 patients treated, 35 emergent malignancies were diagnosed in 25 patients. Of these malignancies, 6 were basal cell carcinomas and 17 were SCCs. In the first placebo-controlled studies, overall rates of malignancy were 1.3% in the treated patients (11 of 876) versus 0.5% in the placebo group (2 of 413).⁵¹ In a report of 201 patients, 7 malignancies were reported in 5 patients, including 3 SCCs and 1 basal cell carcinoma.⁵² However, in a randomized

trial from Lebwohl and colleagues, a specific claim of no increased incidence of malignancy is made.⁵³ To our knowledge, no other dermatologic side effects have been noted with the use of alefacept.

Pruritus

In initial clinical trials of infliximab, pruritus was reported as a substantial side effect, with a rate of 8% (vs. 2% for placebo) in the treatment of RA and a rate of 5% (vs. 2% for placebo) in the treatment of CD.⁶ In clinical practice, the manifestation of clinically relevant pruritus may be less than this; in a study by Flendrie and colleagues, only 1 of 289 patients reported clinically relevant pruritus.⁷ In a study of cutaneous effects in 150 patients using TNF- α inhibitors, no note was made of pruritus as an independent issue.⁸ Pruritus is listed as a possible side effect in the package insert of etanercept, although no published statistics indicate pruritus as an established side effect.⁵

Reported rates of pruritus with rituximab in treatment of lymphoma vary widely; reports of incidence range from no cases reported^{21,25-27} to 20% of treated patients.⁵⁴ The studies on RA indicate a lower incidence of pruritus. The study by Cohen and colleagues showed only 2% experiencing significant pruritus with the first treatment and none with the second.²² Our research did not reveal any patients who had to discontinue use of the drug due to pruritus.

With alefacept, pruritus occurred with an incidence of 11% in placebo patients, 14% at 10 mg, and 16% at 15 mg.⁵³ The only other large-scale report of patient experience that mentions pruritus is a report of 3 years' experience with 201 patients, in which only 4 patients noted the problem.⁵²

Granulomatous Disease

Cases of cutaneous granulomatous disease originally came forward as case reports (Table 4). Subsequently, investigators carried out a study that looked at 199 RA patients and 127 patients with spondyloarthropathy treated with TNF- α antagonists for skin lesions resembling granuloma annulare. Of these patients, 9 (4.5%) of the patients with RA and none of the patients with spondyloarthropathy manifested such lesions. The drugs implicated were infliximab in 2 of 123 patients, adalimumab in 6 of 57 patients, and etanercept in 1 of 17 patients. The time to onset of the lesions was within the first year in seven cases and in the second year in the other two.⁵⁵ Figure 3 a and b is an example of granulomatous reaction from our experience.

Lichenoid Drug Reaction

Nine cases of lichenoid reaction have been reported^{7,56-60} and are summarized in Table 4. Most of the cases of lichenoid eruption resolved whether or not the TNF- α inhibitor was discontinued, leaving the association between the medication and disease process unclear.

Acne

There is some evidence of increased rates of acne with the use of efalizumab in placebo-controlled trials. Summary data from double-blind placebo-controlled trials of efalizumab (1 mg/kg/week) with 1,928 patients noted an increase in the rate of acne among those taking efalizumab (1% vs 4%).⁶¹

There have been no controlled trials that suggest increased rates of acne with the TNF- α inhibitors, although there have been three case reports of infliximab-induced acne.^{62,63}

Table 4. Lichenoid and Granulomatous Reactions

Reaction	Case Reports	Inciting Agents	Disease	Outcome	Time Frame
Lichenoid drug reaction ^{7,56-60}	9	I (3) E (3) A (2) Lenercept (1)	RA (6) AS (1) PsO (1) PsA (1)	Discontinued in 2 cases and both restarted; only one redeveloped lesions	Mean time to onset: 3 mo Median time to onset: 1.5 mo
Granulomatous reaction ^{57,83,84}	9	I (5) E (1) A (1) Lenercept (1) I and E (1)	RA(6) PsA(2) Multiple myeloma (1)	Discontinued in 5 cases (lesions resolved); continued in 4 cases (lesions continued)	In the majority of patients, the reaction occurred within three months of the initiation of therapy, but never prior to three weeks.

A = adalimumab; AS = ankylosing spondylitis; E = etanercept; I = infliximab; PsA = psoriatic arthritis; PsO = psoriasis; RA = rheumatoid arthritis.

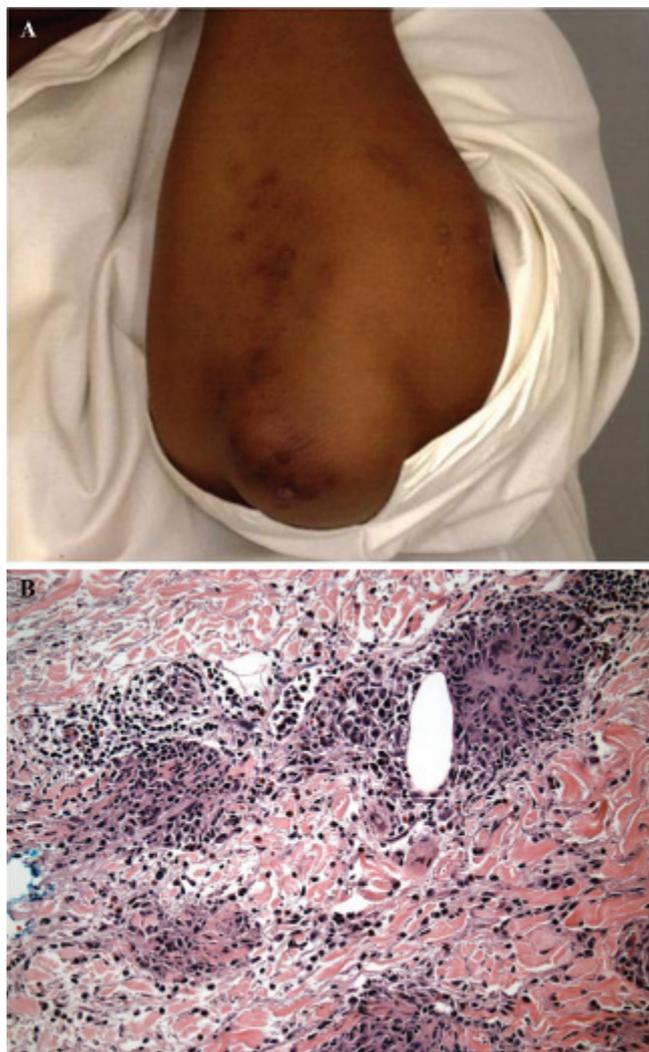


Figure 3. A, Interstitial granulomatous dermatitis in a patient with Chron's disease being treated with infliximab. This was an asymptomatic, slowly progressing skin change. B, Histologies of IGD revealing numerous, non-caseating dermal granulomas (H and E 200 \times).

Progressive Multifocal Leukoencephalopathy

One possible side effect that requires discussion despite its lack of dermatologic findings is progressive multifocal leukoencephalopathy (PML) associated with rituximab and efalizumab. Recently, an exhaustive review of all patients who developed PML after treatment with rituximab was undertaken after case reports of two patients with systemic lupus erythematosus and one patient with RA who developed PML after receiving rituximab were published.⁶⁴ Although there were prior case reports associating PML with rituximab, rituximab's prior use in the treatment of B-cell lymphoproliferative disorders made the implication of the role of rituximab less clear. The median time from last rituximab dose to

PML diagnosis was 5.5 months in this study, and of note, there was found to be an increased rate of mortality in patients who had received rituximab within 3 months of their diagnosis of PML (100% vs 84%). Regarding efalizumab, three confirmed case reports have surfaced: those of a 73-year-old woman, a 70-year-old man, and a 47-year-old man, all treated with efalizumab for plaque psoriasis for more than 3 years, with the first reported case in October 2008.^{65,66} This is of particular concern as only approximately 1,100 patients had been using efalizumab for more than 3 years as of February 2009.⁶⁶ However, it is important to note that, given the confounding of the lymphoproliferative malignancies treated with rituximab and the low numbers of cases with efalizumab, more data will be necessary to establish the degree of correlation.

Unique Cases

There have been a number of case reports of various cutaneous problems hypothesized to be related to the use of TNF- α inhibitors and efalizumab; these are listed in Table 5. Currently, there is no statistical correlation with any of these reported conditions.

Summary

As more experience is gained with monoclonal antibodies, we are simultaneously gaining knowledge about their various cutaneous side effects. Double-blind placebo-controlled trials continue to give an unclear picture of rates of infection with TNF- α inhibitors; however, there is some evidence of increased rates of herpes simplex and zoster infection with rituximab and efalizumab. With regard to malignancy, there is currently no convincing evidence of increased rates with the use of TNF- α inhibitors, rituximab, or efalizumab, although there is some evidence of increased rates of malignancy with alefacept. Whereas trials indicate pruritus to be a side effect of the TNF- α inhibitors, rituximab, and alefacept, published reports do not indicate this to be a common patient complaint or reason for discontinuation of the drugs. Additionally, some small trials indicate that granuloma annulare may be an occasional side effect of TNF- α inhibitors and that acne may be brought on by the use of efalizumab.

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Table 5. Unique Case Reports of Cutaneous Adverse Reactions to Tumor Necrosis Factor- α Inhibitors

<i>Cutaneous Process</i>	<i>Age (Sex)</i>	<i>Disease Being Treated</i>	<i>Biologic Agent</i>	<i>Time to Onset from Initiation of TNF-α Inhibitor</i>	<i>TNF-α Continued?</i>	<i>Therapy</i>	<i>Resolution of Rash?</i>
Perniosis-like eruption ⁵⁶	68 (f)	RA	Infliximab	6 infusions	Yes	NA	NA
Acute folliculitis ⁵⁶	36 (f)	PsA	Infliximab	1 yr	Yes	Topical corticosteroids	NA
Dermatomyositis ⁸⁵	52 (f)	RA	Lenercept	2.5 mo	No	None	Yes
Dermatitis herpetiformis ⁸	62 (f)	RA	Adalimumab	6 mo	NA	NA	NA
Pityriasis rosea ⁸	76 (f)	RA	Adalimumab	26 mo	NA	NA	NA
Dermatitis sicca ⁸	63 (m)	RA	Infliximab	1 mo	NA	NA	NA
Alopecia areata ^{8,86-90}	23 (f), 37 (m), 43 (m), 23 (f), 51 (f), 49 (m)	RA (4), AS, PsO (2),	Adalimumab (2), infliximab (3), etanercept	3 infusions, 7 mo, 4 infusions, 2 mo, 11 mo, 2 yr	NA (3), yes (1), no (2)	NA (3), clobetasol 0.05% (2), topical dexamethasone and topical 5% minoxidil	NA, none (3), complete, slight improvement
Androgenic alopecia ⁸	39 (f)	RA	Adalimumab	8 mo	NA	NA	NA
Superficial perivascular dermatitis: drug eruption ⁹¹	41 (f)	RA	Adalimumab	1 wk	No	Topical corticosteroids	Resolved within 10 days of discontinuation
Vitiligo ⁹²	66 (m)	PsO	Adalimumab	5 mo	Yes	NA	No resolution
Bullous eruption ⁹³	72 (m)	RA	Infliximab	4th infusion	NA	Prednisone taper initiated at 60 mg/d	Complete
Subacute cutaneous lupus erythematosus ⁹⁴	65 (f)	Lichen planus	Efalizumab	8 wk	Yes	Hydroxychloroquine	Complete
Lichen simplex chronicus/dermatitis ⁹⁵	48 (m)	PsO	Efalizumab	9 wk	Yes	UVB, topical betamethasone	Complete
DRESS syndrome ⁹⁶	52 (m)	PsO	Efalizumab	4 wk	Yes	Prednisone	Improved
Pityriasis rubra pilaris ⁹⁷	60 (f)	PsO	Efalizumab	9 wk	Yes	Oral corticosteroids, acitretin (30 mg/d), PUVA therapy	Improved

AS = ankylosing spondylitis; DRESS = drug rash with eosinophilia and systemic symptoms; f = female; m = male; NA = not applicable; PsO = psoriasis; PUVA = psoralen plus ultraviolet A; RA = rheumatoid arthritis; UVB = ultraviolet B.

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