Biologic Agent-Associated Cutaneous Adverse Events: A Single Center Experience

Rahul Sehgal, MD; Erik J. Stratman, MD; and Jonathan E. Cutlan, MD

Biologic agents are regarded as an effective treatment for a variety of autoimmune diseases. These drugs have an acceptable safety and tolerability profile, although an increasing number of autoimmune conditions have been reported with their use. Additionally, a variety of cutaneous diseases have been associated with their use. Here we report our experience of adverse cutaneous events with the use of biologic agents. An alternative explanation for patients presenting with adverse cutaneous events including drug interactions must be carefully investigated.

Keywords: Adverse drug events; Anti-TNF therapy; Autoimmune disease; Biologic agents; Cutaneous vasculitis

Biologic agents (aka. biologics) are genetically-engineered proteins derived from human genes designed to reduce inflammation by inhibiting specific components of the immune system that can cause inflammation. Biologics are used in treating a wide variety of autoimmune diseases and have become mainstays in the management of rheumatoid arthritis (RA), ankylosing spondylitis, psoriasis, psoriatic arthritis (PsA), and inflammatory bowel disease (IBD). These agents have an acceptable safety and tolerability profile, although an increasing number of autoimmune conditions related to their use have been reported.¹ A variety of cutaneous diseases are also reported as being induced by biologic agents.² In a large prospective study of patients with RA, 25% of those on tumor necrosis factor- α inhibitor (TNF-I) therapy required a dermatological consultation, compared with 13% among a TNF-I naïve group.³ Skin infections, eczema, and drug-related eruptions are the most common cutaneous adverse events reported. Immune-mediated skin lesions attributed to use of biologic agents include psoriasis, granuloma annulare, cutaneous vasculitis, alopecia areata, cutaneous lupus erythematosus, lichen planus, hidradenitis suppurative, cutaneous sarcoidosis, and vitiligo.⁴ Psoriasis is the most often reported of these immune mediated skin lesions.⁵

We report, herein, our experience with cutaneous adverse events associated with the use of biologic agents.

Case I

A man, aged 58 years, presented with a 6-month history of an acute onset bright red skin rash. His chronic psoriasis and PsA had been under control with etanercept monotherapy for the past 15 years. The newer eruption consisted of a partially blanchable, confluent dusky red patch extending over 30 cm, from just below the umbilicus to the superior abdomen with extension on to the lateral abdomen, groin, and scrotum (Figure 1, panels A and B). His serologic profile was negative for rheumatoid factor (RF) and anti-cyclic citrullinated peptide antibody (ACPA). Antinuclear antibody (ANA) was weakly positive at a titer of 80. Erythrocyte sedimentation rate (ESR) was 27 mm/h (range 0-13 mm/h); C-reactive protein (CRP) was 0.2 mg/dL (range $\leq$ 1.0 mg/dL). The patient underwent two punch biopsies showing a moderately dense superficial to deep perivascular and interstitial, predominantly neutrophilic infiltrate with occasional eosinophils, no vasculitis, and no alteration of dermal collagen (Figure 2, panels A and B), consistent with a neutrophilic dermatosis (ND). Aerobic, fungal, and mycobacterial tissue cultures were negative. A series of treatments were attempted, including oral prednisone,

Corresponding Author: Rahul Sehgal, MD, Mayo Clinic Health System-Eau Claire, Department of Rheumatology, 1400 Bellinger Street, Eau Claire, WI 54702 USA, Email: Sehgal.rahul@mayo.edu

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dapsone, and colchicine without resolution of the eruption. These treatments and etanercept were then discontinued. The patient was started on treatment with adalimumab for worsening psoriatic arthritis with good clinical response. His skin condition completely resolved within 8 weeks without flare-up of psoriatic arthritis or psoriasis. No recurrence of skin rash has been observed over the subsequent year (Figure 1, panels C and D).

Figure 1. (A, B) Cutaneous rash while on etanercept. (C, D) 8 weeks after discontinuation of etanercept and initiation of adalimumab the rash has disappeared.

Case 2

A woman, aged 65 years, with a >30 year history of nodular and erosive RA presented with a new rash. She had a history of active RA with a routine assessment of patient index data 3 score of 24. Her serologic profile was strongly positive for RF at a titer of 1:1280 (nL<1:80), ACPA >300 (nL<2.9), ANA 1:80, ESR 67 mm/h, and CRP 4 mg/dL. In view of her persistent RA activity despite previous methotrexate and hydroxychloroquine therapy, certolizumab pegol injection was initiated. Within 20 hours of initiating treatment, non-blanching, violaceous-red pinpoint to 0.3 cm petechial and purpuric macules appeared on dorsal feet extending up to shins/calves, thighs, medial buttocks, and supra-pubic area (Figure 3, panels A and B). Biopsy of the left medial dorsal foot showed prominent extravasated red blood cells with associated neutrophils, leukocytoclasia, and perivascular deposition of immunoglobulin [IG]-G, IG-M, complement-3, and fibrinogen on direct immunofluorescence (DIF) consistent with leukocytoclastic vasculitis (Figure 4). Her renal function remained normal (creatinine 0.9 mg/dL). Certolizumab was discontinued, and the skin symptoms resolved over the next 10 days. The patient has since been managed with combination treatment comprised of methotrexate, hydroxychloroquine, and low dose leflunomide, which has maintained adequate control of her RA without recurrence of cutaneous lesions. Interestingly, a previous trial of adalimumab 3 years prior had resulted in acute sarcoidosis with shortness of breath, new onset hilar/mediastinal lymphadenopathy, and progressive, confluent, non-blanchable, macules, petechial, and purpuric eruption on the abdomen extending onto the pelvis, lower back, buttock, feet, and lower legs. A mediastinal lymph node biopsy (Figure 5, panels A and B) confirmed non-caseating granuloma consistent with sarcoidosis. An evolving perivascular granulomatous inflammation was noted on a skin biopsy from her leg. Adalimumab was thereafter discontinued with gradual resolution of skin lesions.

Figure 2. (A) Biopsy of the left lateral abdomen shows mild superficial dermal edema and interstitial and perivascular inflammation (10X, hematoxylin and eosin). (B) High power image showing that the majority of the inflammatory cells are interstitial and perivascular neutrophils. The blood vessels fail to show vascular damage (20X, hematoxylin and eosin).

Case 3

A woman, aged 29 years, developed numerous red and scaly, round to oval plaques over her back, breasts, inframammary and infrapannus regions, and legs (Figure 6, panels A, B, C) after 3 weeks of receiving tocilizumab treatment for Takayasu arteritis. She was diagnosed 6 years earlier in the setting of resistant hypertension, absent left forearm pulse, and marked elevation of acute phase reactants (ESR 85 mm/h; C-reactive protein 11 mg/dL). She had extensive disease and was found to have external carotid, renal, subclavian, celiac, and vertebral artery inflammation and obstruction. She was previously treated with methotrexate, azathioprine, infliximab, rituximab and high dose systemic corticosteroids. Tocilizumab was initiated as a steroid sparing alternative. The skin lesions worsened after her second infusion of tocilizumab. Skin biopsy showed features of psoriasiform epidermal hyperplasia, confluent parakeratosis, loss of granular layer and dilated blood vessels within dermal papillae consistent with a diagnosis of psoriasis (Figure 7). Tocilizumab treatment was discontinued. Psoriasis was treated with topical steroids and narrow band ultraviolet B therapy with improvement. Ustekinumab was started for vasculitis progression, resulting in resolution of skin psoriasis and vasculitis.

Discussion

The cases we describe include two unique patients on TNF-I therapy who developed unusual drug-associated adverse cutaneous eruptions including ND associated with etanercept therapy, cutaneous vasculitis associated with use of certolizumab therapy, and psoriasis occurring in a patient with Takayasu arteritis treated with tocilizumab. A variety of immune mediated reactions and other adverse events have been reported with use of biologic agents. Cutaneous manifestations are most common among these adverse events. In majority (80%) of cases, these adverse events represent a new disease while in some (20%) they are exacerbations of pre-existing disease.⁶ In a prospective study,

Figure 3. Figure showing extent and distribution of cutaneous vasculitis lesions on (A) the foot and (B) inner thigh of the patient on certolizumab.

Figure 4. Biopsy of the left medial dorsal foot shows prominent extravasated red blood cells with associated neutrophils with leukocytoclasia and perivascular fibrin deposition, consistent with a leukocytoclastic vasculitis (20X, hematoxylin and eosin).

Figure 5. (A, B) Sections of the mediastinal lymph node show diffuse non-necrotizing granulomatous inflammation, consistent with sarcoidosis. Special stains [(A) GMS and (B) FITE] were negative for micro-organisms.

Table 1. Medications associated with neutrophilic dermatoses¹²

All-transretinoic acid
Carbamazepine
Celecoxib
Diazepam
Diclofenac
Granulocyte colony-stimulating factor
Levonorgestrel / ethinyl estradiol
Hydralazine
Minocycline
Nitrofurantoin
Propylthiouracil
Trimethoprim–sulfamethoxazole

dermatological events resulted in withdrawal of TNF-I therapy in 26% of patients with RA.³ Other than infusion/injection site reactions, psoriasis and psoriasiform-like lesions, lupus-like syndromes, cutaneous vasculitis, and cutaneous infections have the strongest association with TNF-I treatment. These are followed by eczematous reactions, lichenoid disorders, and granulomatous reactions. There has not been an association with use of TNF-I treatment and cutaneous lymphoma, epithelial skin cancers or melanoma.⁷ Cutaneous reactions such as infusion reactions and injection site reactions can be directly attributed to the administration of TNF-I therapy. However, a direct association with use of TNF-I and other cutaneous reactions is not always obvious.

The patient reported in case 1 developed ND while on etanercept therapy. Neutrophilic dermatoses (ND) are a group of diseases including Sweet syndrome (SS), pyoderma gangrenosum (PG), subcorneal pustular dermatosis (SPD), and erythema elevatum diutinum.⁸ As the name implies, ND are characterized by a dense inflammatory infiltrate composed of neutrophils in absence of infection. A number of systemic disorders such as RA, systemic lupus erythematosus, dermatomyositis, systemic sclerosis, IBD, myeloproliferative disorders, monoclonal gammopathy and auto-inflammatory diseases are associated with development of ND. A wide variety of drugs⁹ have also been implicated with development of SS. Granulocyte colony stimulating factor (G-CSF) is considered most common among them while other drugs include minocycline, trimethoprim/sulfamethoxazole, HRT/OCP, furosemide, celecoxib, azathioprine.¹⁰ TNF-I have also been associated with development of SS^{11,2} and PG lesions.¹² Similar unexpected reactions have been described with infliximab use in UC¹³ and RA¹⁴ (Table 1).

The occurrence of ND in our patient on etanercept treatment cannot be attributed to class effect of TNF-I therapy, since adalimumab, etanercept and infliximab have been used successfully in managing refractory PG associated with IBD.^{15,16} Neutrophilic dermatosis (ND) and especially SS have also been successfully treated with TNF-I such as etanercept

and infliximab.¹⁷ Success with use of TNF-I has been rather variable in SPD. The treatment achieved complete remission in one case¹⁸ while the results were temporary in another case.¹⁹

A lack of response to systemic treatment in our case 1 and skin improvement upon etanercept discontinuation with a switch to adalimumab favors its association with etanercept use. The pathophysiology of ND is poorly understood. An underlying role of activated T lymphocyte in recruitment of neutrophils to the dermis has been postulated.

Cytokine expression in skin of PG and SS patients compared with healthy controls show an increased expression of IL-1, IL-8, IL-17, TNF-alpha, MMP-2, MMP-9, IFN- γ , and G-CSF.²⁰

Cutaneous vasculitis as described in our case 2 has been reported with TNF-I therapy (especially etanercept and infliximab) in RA patients.^{21,22} Although a direct causal relationship of drug use with cutaneous vasculitis is difficult to establish, a close temporal association of vasculitis with initiation of TNF-I therapy and its resolution upon discontinuation of the drug aids in this distinction. The pathogenesis of cutaneous vasculitis occurrence is hypothesized to be a type 3 hypersensitivity reaction triggered by anti-TNF- α :TNF- α immune complex deposition in small capillaries and the induction of complement activation.²³ Management of cutaneous vasculitis in majority of affected patients involves discontinuation of the offending drug, in this case the TNF-I therapy, and rarely necessitates additional immunosuppressant use.

Tocilizumab, a humanized monoclonal antibody directed against IL-6 receptor is FDA-approved for treatment of RA.²⁴ A variety of cutaneous adverse events associated with tocilizumab have been described. New onset and worsening psoriasis has been rarely described in patients receiving tocilizumab.²⁵⁻²⁷ Our patient developed *de novo* psoriasis 3 weeks after the first infusion of tocilizumab, which worsened after the second infusion, prompting discontinuation of drug. Non-psoriatic cutaneous reactions in tocilizumab users including erythroderma, lupus-like syndrome, cutaneous vasculitis, palmoplantar pustulosis, purpuric eruptions, and atopic dermatitis have also been described.^{24,28} Onset of psoriasis with tocilizumab is an unexpected adverse event, as IL-6 is considered to contribute to the pathogenesis of psoriasis via Th17 cells and the resultant downstream effect on production of various cytokines (IL-17, IL-22, IL-6, TNF- α).^{29,30} Other biologic agents such as rituximab³¹ and abatacept³² have also been associated with new onset or worsening psoriasis.

Conclusion

Alternative explanations for an adverse cutaneous event must be carefully investigated when confronted with a suspected new, atypical, or paradoxical adverse event. These include

Figure 6. Red and scaly discoid lesions (A) over back, (B) under breasts and (C) under the pannus in patient on tocilizumab.

Figure 7. Sections showing psoriasiform epidermal hyperplasia with neutrophilic parakeratosis. There is suprapapillary plate thinning with prominent dermal blood vessels within dermal papillae and superficial perivascular lymphocytic infiltrate within the dermis. These findings would be in keeping with the histologic findings of psoriasis.

cutaneous manifestation of underlying disease, infusion/injection site reactions, immune-mediated skin lesions, skin infections, eczema, and concomitant medication use. A broad range of cutaneous eruptions have been reported in patients undergoing TNF-I therapy. The pathophysiologic mechanism that triggers development of paradoxical reactions such as psoriasis is poorly understood. A close temporal relationship of the presentation and resolution of cutaneous adverse events with use and withdrawal of TNF-I therapy, respectively, is important in distinguishing a drug-induced eruption from a distinct primary process. Treatment approach is tailored to the

severity of each cutaneous eruption, although discontinuation of the suspected biologic agent is a reasonable first step. Because the spectrum of adverse cutaneous events in biologic agent users continues to expand with the growing number and wider use of available biologic therapies, there is need for a greater awareness among treating physicians.

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Author Affiliations

Rahul Sehgal, MD*; Erik J. Stratman, MD†; Jonathan E. Cutlan, MD‡

*Mayo Clinic Health System, Department of Rheumatology, Eau Claire, WI 54702 USA

†Marshfield Clinic Health System, Department of Dermatology, Marshfield, WI 54449 USA

‡Marshfield Clinic Health System, Department of Pathology, Marshfield, WI 54449 USA