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PSORIASIFORM AND ECZEMATOUS PARADOXICAL REACTIONS TO BIOLOGIC AGENTS

Introduction

Biologics, a class of therapeutic monoclonal antibodies (mAbs), have formed the cornerstone for treatment of many systemic diseases and conditions in the fields of rheumatology and dermatology.^{1,2} These agents have demonstrated strong efficacy profiles in clinical trials, with numerous new agents being approved in the past few years. However, it is important to note that some patients being treated with biologics may experience paradoxical reactions (PRs), which refers to the new occurrence or worsening of pre-existing immune-mediated conditions following initiation of the drug.¹ True paradoxical reactions involve the development of immune-mediated diseases with the use of biologic agents that are typically utilized to treat the idiopathic form of the drug-induced reaction.² This article aims to summarize the literature on psoriasiform and eczematous PRs to biologics.

Psoriasiform Paradoxical Reactions

TNF-alpha inhibitors

Psoriasiform PRs are commonly reported in association with tumor necrosis factor (TNF) therapy, which is widely used for the management of inflammatory conditions such as moderate-to-severe psoriasis and inflammatory bowel disease (IBD).³ The incidence of paradoxical psoriasis in patients receiving anti-TNF- α treatment varies from 3.8% to 10%, with infliximab (>50%), adalimumab (30%) and etanercept (11%) accounting for the majority of the cases respectively. Onset time between initiation of the treatment and emergence of the PR is extremely variable and can range from one month to 10 years from the start of treatment, with an average of 16.4 years.⁴ A summary of paradoxical psoriasis incidence with biologic agent exposure appears in **Table 1**.

While most cases represent new-onset development of psoriasis, paradoxical exacerbations and morphological transitions have been reported with

Drug Classes	General Information	Presentation and Morphology	Relative Latency	Management
TNF- α inhibitor	Incidence varies from 3.8% to 10% Cases associated with infliximab (>50%), adalimumab (30%) and etanercept (11%)	May resemble plaque, palmoplantar pustular, guttate, inverse and generalized/pustular psoriasis Higher incidence of palmoplantar involvement compared to classical form of psoriasis	1-10 months range, average of 16.4 years.	Systematic review of IBD patients: majority of patients who switched to different drug class (e.g., ustekinumab) reported complete clearance. Less resolution in patients who switched to a different anti-TNF- α agent. Retrospective cohort study in pediatric patients: majority of patients continued treatment with topical corticosteroid and steroid-sparing adjuvant therapies for management of PR.
IL-17 inhibitor	Most cases associated with secukinumab, followed by brodalumab and ixekizumab treatment respectively.	May resemble plaque psoriasis, palmoplantar psoriasis, generalized pustular psoriasis, and inverse psoriasis.	1-16 months range, average of 4.9 months.	Most patients were resistant to topical treatments. Varying responses to systemic treatments (e.g., brodalumab, cyclosporin A, methotrexate). In some cases, secukinumab treatment was discontinued due to the adverse reaction, with successful resolution. ⁸
IL-12/23 p40 inhibitor	Most cases associated with secukinumab, followed by brodalumab and ixekizumab treatment respectively.	Common morphological presentations were plaque psoriasis and palmoplantar psoriasis Generalized pustular psoriasis also observed	Average time to onset of 3 months	Targeted treatments and ustekinumab discontinuation in most cases, leading to resolution. ⁸
IL-4Ra inhibitor	Dupilumab is currently the only approved IL-4Ra inhibitor	Most cases presented as plaque psoriasis and palmoplantar psoriasis lesions Some resembled guttate, erythrodermic, scalp and pustular psoriasis Lesions identical to idiopathic disease; described as well-demarcated and erythematous scaly plaques	Average of 4.3 months and 3.3 months for new-onset and exacerbation respectively	Patients received topical corticosteroids, vitamin D analogues with successful resolution. In severe or refractory cases, dupilumab was discontinued in favour of other immunomodulating agents and systemic treatments (e.g., JAK inhibitors).

Table 1. Paradoxical psoriasis with biologic agent exposure; courtesy of Asfandiyar Mufti, MD.

the use of anti-TNF- α treatment for psoriasis. With respect to morphology, psoriasiform PRs seen with these agents typically resemble plaque, palmoplantar pustular and guttate lesions, but other reactions such as inverse and generalized/pustular psoriasis may also occur.⁵ A systematic review analyzing 207 published cases of TNF- α inhibitor-induced psoriasiform eruptions observed that these drug-induced PRs involved a higher incidence of palmoplantar involvement compared to the classical idiopathic form of psoriasis. Moreover, multiple concomitant morphologies may be present in individual patients, with 15% of cases presenting with more than one type of lesion.^{5,6} Histologically, anti-TNF- α -associated psoriasiform PRs have generally demonstrated the typical findings of classical psoriasis, which are characterized by epidermal hyperplasia and lymphocyte infiltrates, dilated capillaries and

parakeratosis.⁶ However, there have been reports of uncharacteristic findings such as spongiosis and the presence of eosinophils and plasma cells, which may be used to distinguish from primary psoriasis.⁷

With respect to management, a systematic review of TNF- α -induced paradoxical PR treatment outcomes in IBD patients who switched to different biologic therapies reported several key findings. Among the patients who switched to a different anti-TNF- α agent, only 39.2% reported resolution of symptoms. However, when switching to a different class of biologic therapy, such as ustekinumab or vedolizumab, the majority of patients experienced complete resolution.⁷ Conversely, in a retrospective study, in a cohort of children under the age of 18 who developed new-onset PR while taking a TNF inhibitor for a non-dermatologic disorder, the majority of

patients were able to continue TNF inhibitor therapy with topical corticosteroids and non-corticosteroid adjuvant therapies for the management of symptoms.⁸ Further research is needed to explore management and treatment outcomes in the context of patients receiving anti-TNF- α agents for inflammatory skin diseases such as psoriasis.

IL-17 inhibitors

The therapeutic potential of anti-IL-17 agents has been explored in recent clinical trials and studies. Although there is limited literature reporting the development of psoriasiform PRs in response to anti-IL-17 treatment, the few cases that have been described are primarily associated with secukinumab, followed by brodalumab and ixekizumab treatment respectively. The average onset time to presentation of paradoxical psoriasis is 4.9 months and ranges from 1–16 months following initiation of anti-IL-17 treatment.⁴

Secukinumab selectively binds to and neutralizes IL-17A, a pro-inflammatory cytokine that is believed to play a key role in driving the pathogenesis of psoriasis. However, despite being approved for the treatment of psoriasis, several cases of new-onset development and exacerbation of psoriasis have been observed in patients treated with this agent. Clinical presentation manifested in a range of morphological phenotypes including plaque psoriasis, palmoplantar psoriasis, generalized pustular psoriasis, and inverse psoriasis. Larger-scale studies are needed to draw comparisons regarding the frequency of morphological presentations between IL-17-associated PRs and idiopathic psoriasis.⁹

Most patients were resistant to topical treatments and had varying responses to systemic treatments such as infliximab, brodalumab, cyclosporin A and methotrexate. In some cases, secukinumab treatment was discontinued due to the adverse reaction.⁹

IL-12/23 p40 inhibitors

Given that ustekinumab is currently the only approved p40 inhibitor,¹ there is limited literature available on the association of paradoxical psoriasis with IL-12/23 inhibitors. This agent blocks the shared p40 subunit on IL-12 and IL-23 cytokines, both of which contribute to the inflammatory symptoms seen with psoriasis. Although ustekinumab has been in use since 2009 and is approved for the treatment of psoriasis, psoriatic arthritis and IBD, only nine reported cases of associated psoriasiform PR have been described. Among these patients, four cases involved the new-onset development of psoriasis, and five cases involved the exacerbation of pre-existing

psoriasis.⁹ Although it is difficult to draw conclusions from a small body of data, the average onset time to the presentation of psoriasiform PR was within three months of ustekinumab treatment initiation.¹

Similar to the psoriasiform PRs associated with other biologic treatments, ustekinumab-induced paradoxical psoriasis manifested as various clinical phenotypes. Along with the common morphological presentations such as plaque psoriasis and palmoplantar psoriasis, generalized pustular psoriasis was observed in five cases and two of these had new-onset development. In the majority of the patients, ustekinumab treatment was discontinued along with targeted treatments for the PR, leading to improvement in or resolution of the psoriasiform lesions.⁹

IL-4Ra inhibitors

As with ustekinumab, dupilumab is the first and, currently, the only approved agent in its drug class. It has been associated with marked symptomatic improvement in clinical trials focusing on atopic dermatitis (AD), asthma and other indications. Dupilumab targets the alpha-subunit of IL-4 receptor, subsequently inhibiting the IL-4 and IL-13 signalling pathways, which are implicated in the pathogenesis of AD.¹⁰

In a review summarizing all known cases of dupilumab-associated psoriasis, the average time to onset of psoriasiform PRs was 4.3 months and 3.3 months post-treatment initiation for new-onset and exacerbation of pre-existing psoriasis respectively. Similar to cases of classical psoriasis, most cases of dupilumab-associated psoriasis presented as plaque psoriasis and palmoplantar psoriasis lesions.¹ The presentation of the lesions have been described as well-demarcated and erythematous scaly plaques, which is identical in appearance to the idiopathic form of the disease.¹⁰ A smaller proportion of dupilumab-induced cases manifested as guttate, erythrodermic, scalp, and pustular psoriasis.^{1,10} Interestingly, although dupilumab is not typically employed for the treatment of psoriasis, in three patients with pre-existing psoriasis, a flare of the disease was observed. In these patients, the exacerbation was severe in nature and was characterized by a shorter time to onset.¹⁰ Upon skin biopsy, histological findings resembled features characteristic of classical psoriasis such as parakeratosis and lymphocyte infiltration of the dermis. However, mild spongiosis and the presence of eosinophils were also observed and may serve as distinguishing features between the two causes of psoriasis.^{1,10} Approximately half of the patients in this

Drug Classes	General Information	Presentation and Morphology	Relative Latency	Management
TNF- α inhibitor	Cases associated with infliximab (70%), followed by adalimumab (24.5%) and other agents	Clinical morphology included erythematous plaques, papules and excoriations affecting the face, neck, trunk and limbs	Average time of 22.7 months	Anti-TNF treatment was rarely discontinued, and eczema was successfully managed with emollients as well as topical corticosteroids in more severe cases
IL-17 inhibitor	Overall incidence of 72.55%, majority associated with secukinumab (52.94%), followed by ixekizumab (19.61%)	Range of clinical presentations: classic generalized AD, facial dermatitis and dyshidrotic eczema	4 months	Eczematous PRs were managed primarily with topical corticosteroids In severe or refractory cases, anti-IL-17 treatment was discontinued Case series including patients receiving brodalumab for psoriasis: all patients were switched to risankizumab directly or received cyclosporin and apremilast prior to risankizumab, and achieved complete clearance of lesions
IL-23 p19 inhibitor	4 identified cases: 2 associated with guselkumab and risankizumab respectively	Clinical presentation consistent with eczema: erythematous plaques, scaling and excoriations Histological findings consistent with eczema: acanthosis, spongiosis and perivascular lymphocytic infiltrate	Range of 3 weeks to 4 months	Severe case was unresponsive to topical corticosteroid treatment, and required discontinuation of guselkumab and administration of tar preparation One risankizumab case was switched to alternative anti-psoriatic agent ustekinumab and received topical corticosteroids with successful improvement of lesions
IL-4Ra inhibitor	Dupilumab is currently the only approved IL-4Ra inhibitor	Commonly appeared as a localized dermatitis reaction affecting the face and/or neck regions	Insufficient data available	Discontinuation of dupilumab led to improvement in and resolution of symptoms in majority of cases

Table 2. Paradoxical eczema with biologic agent exposure; courtesy of Asfandyar Mufti, MD.

review continued with dupilumab treatment. They received primarily topical corticosteroid treatments and experienced improved clearance of skin symptoms. In severe or refractory cases, dupilumab use was discontinued with recourse to other immunomodulatory agents and systemic treatments, including Janus kinase (JAK) inhibitors such as baricitinib and upadacitinib.¹⁰

Eczematous Paradoxical Reactions

TNF- α inhibitors

Following psoriasis, eczematous reactions are the second most common PR associated with anti-TNF- α treatment and have been observed in the management of various rheumatological conditions.^{1,5} Within this drug class, infliximab was responsible for the largest proportion of cases (70%), followed by adalimumab (24.5%) and other agents. The average

time to onset of eczematous PR was 22.7 months following the initiation of anti-TNF- α treatment.⁴

It is worth noting that there have also been several reports of a phenotypic switch to eczema in patients receiving biologic agents such as TNF-inhibitors for psoriasis. In this study, a prior history of eczema/AD was described in 11 of the 24 cases (46%). Similar to cases of eczema development in patients being treated with TNF-inhibitors for indications other than psoriasis, the clinical morphology included erythematous plaques, papules and excoriations affecting the face, neck, trunk and limbs.¹¹

Data specific to treatment outcomes of eczematous lesions from different management strategies is scarce as information regarding eczema PRs is often pooled with a broader range of dermatologic complications of anti-TNF agents. Regardless, in

these studies, eczematous reactions were successfully resolved with topical treatments such as emollients and topical corticosteroids while continuing use of the initial anti-TNF agent in most patients.¹²

IL-17 inhibitors

Unlike other biologic drug classes which are primarily associated with psoriasiform PRs, eczematous reactions are the most commonly reported PR with anti-IL-17 treatment.¹ A systematic review of patients receiving biologics for psoriasis found that eczematous PRs are more common with IL-17A inhibitors vs other biologics, with an overall incidence of 72.55%; secukinumab accounted for most cases (52.94%), followed by ixekizumab (19.61%) and other agents. All patients in this study responded well to biologic treatment prior to the onset of paradoxical eczema.¹² A summary of paradoxical eczema incidence with biologic agent exposure appears in **Table 2**.

With respect to time to onset, eczematous PRs typically occurred within four months of initiating anti-IL-17 treatment. The clinical spectrum included a range of presentations such as classic generalized AD, facial dermatitis and dyshidrotic eczema. IL-17 inhibitor treatment was discontinued in half of the cases and the eczematous PR was managed primarily with topical corticosteroids.¹

In a case series reporting on three patients who received brodalumab treatment for psoriasis refractory to topical and/or systemic treatments and subsequently developed eczematous reactions, their treatment was either switched to risankizumab directly or they received cyclosporin and apremilast initially before recourse to risankizumab. All of the patients in this study achieved full clearance of skin symptoms.¹³ Eczema was diagnosed clinically in two patients and one patient showed histological findings consistent with eczematized psoriasis upon skin biopsy.

IL-23 p19 inhibitors

IL-23 p-19 inhibitors have rarely been reported in the literature in association with eczematous eruptions, possibly because they have only recently been approved for psoriasis. Of the four identified cases, two involved guselkumab and two involved risankizumab. Of all four cases, three patients had a history of atopy, suggesting that an underlying atopic predisposition increases the risk of eczematous eruptions following treatment.⁵ Among these patients, time to onset of eczematous PR ranged from three weeks to four months. The clinical presentation and histological findings were relatively consistent with eczema: erythematosquamous

plaques, scaling and excoriations upon physical examination, as well as biopsy showing acanthosis, spongiosis and perivascular lymphocytic infiltrate.¹⁴⁻¹⁶ The case reports explicitly mentioned that guselkumab and risankizumab treatment was discontinued in two patients respectively. One patient's eczematous PR was markedly severe, recalcitrant to topical corticosteroids, and required hospitalization for treatment with tar preparation composed of betamethasone dipropionate and salicylic acid, leading to successful resolution. The other patient was switched to ustekinumab for psoriasis management and received topical corticosteroids to treat eczematous symptoms with successful clearance.

IL-4Ra inhibitors

Although dupilumab has been approved for the treatment of AD based on overall efficacy and a positive safety profile, Phase 3 trials of dupilumab have described an exacerbation of AD in 10% to 18% of patients. Eczematous PRs most commonly appear as a localized dermatitis reaction, commonly affecting the face and/or neck regions. Discontinuation of dupilumab led to improvement in and resolution of symptoms in the majority of cases.¹

Conclusion

The mechanism implicated in the development of PRs has not been fully elucidated and may vary depending on the class of biologics used. Anti-TNF- α treatment is the most well-studied in the context of PRs and there are several hypotheses underpinning the pathogenesis of PRs associated with TNF- α -inhibitors. For example, blocking TNF- α may lead to the overproduction of Type 1 interferons by plasmacytoid dendritic cells (pDCs), which can result in the induction or worsening of psoriasiform lesions.^{17,18} With respect to eczematous PRs, several studies have hypothesized that inhibition of TNF alters the cytokine balance and shifts T cell polarization from Th-17/Th-1 subsets to Th-2 mediated signalling. As psoriasis is an inflammatory skin disease that is predominantly Th-1/Th-17 mediated and AD is a Th-2 mediated disorder, this hypothesis explains why many of the patients with psoriasis who received anti-TNF treatment developed paradoxical eczematous reactions.⁵

The primary objective in the management of PRs is to maintain symptomatic relief and control of the underlying disease while treating the emerging PR.¹⁸ As there are no well-established guidelines for managing PRs with biologic treatment, clinicians should closely monitor patients and may refer to

treatment guidelines for classical psoriasis and AD. In the case of TNF-inhibition-associated psoriasis, a study proposed a treatment algorithm initiating the referral of patients to a dermatologist for clinical and histological confirmation of psoriasis.⁶ In mild-to-moderate PRs that present solely as cutaneous symptoms and affect less than 5% of the body surface area, the PR may be managed with topical treatments such as corticosteroids and vitamin D analogues. If more than 5% of the body surface area is affected, phototherapy and systemic treatments such as methotrexate or acitretin may be added to the treatment regimen.¹ However, with severe psoriasiform lesions, involvement of internal organs, erythrodermic presentation, and/or significant detriment to the patient's quality of life (QOL), discontinuation of the biologic agent should be considered given that most PRs have shown to resolve with treatment interruption.²⁰ Additionally, if the underlying disease is not well managed, a switch to a different class may also be beneficial.^{1,6} An understanding of risk factors, such as increased risk of psoriasiform PRs with adalimumab and decreased risk with advanced age, a history of atopic diseases, and other risk factors may be beneficial to clinicians in informing their management plan.²¹ Similar guidelines can be applied to the management of eczematous PR.

Further study of psoriasiform and eczematous PRs with biologic treatment is needed to better understand their pathogenesis, develop more comprehensive treatment guidelines, and facilitate early recognition of these reactions for more effective management.

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Financial Disclosures

None.

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