

# Unintended Consequences of Immune Therapy for Immune-Mediated Diseases: Paradoxical Psoriasis and Dupilumab-Associated Musculoskeletal Syndrome

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**ABSTRACT.** Two presentations at the Group for Research and Assessment of Psoriasis and Psoriatic Arthritis (GRAPPA) 2023 annual meeting focused on unintended consequences of immunomodulatory therapy for psoriasis (PsO). Dr. Elizabeth Wallace presented on unintended consequences of tumor necrosis factor inhibitors for treating PsO and other inflammatory disorders. These consequences include paradoxical PsO, which is defined as unexpected new PsO cases or worsening PsO symptoms seemingly induced by treatment. Dr. Bruce Kirkham focused on unintended consequences of dupilumab treatment, which can include a musculoskeletal syndrome similar to psoriatic arthritis.

**Key Indexing Terms:** adverse drug event, GRAPPA, musculoskeletal pain, psoriasis, psoriatic arthritis, therapeutics

## Introduction

Targeted immunotherapies using monoclonal antibodies or constructs have thankfully had limited adverse event profiles, with adverse events usually related to and limited by their immune actions. Infections such as tuberculosis and listeria were generally slightly increased in patients receiving therapies that neutralize tumor necrosis factor (TNF), but these infections were managed successfully.<sup>1</sup> Dupilumab, which inhibits interleukin (IL)-4 and IL-13, is associated with an increase in helminth/parasitic gastrointestinal infections,<sup>2</sup> whereas IL-17 inhibitors (IL-17i) are associated with a slight increase in mild fungal infections.<sup>3</sup> This is in keeping with the known functions of type 2 and type 17 immune-mediated pathways. Unexpected immune-mediated syndromes have also been recognized with most of these targeted therapies. Induction of autoantibodies was noted in early infliximab studies,<sup>4</sup> and as TNF inhibitors (TNFi) became more widely used, drug-induced systemic lupus erythe-

matusus was clinically detected.<sup>5</sup> Here we present 2 types of unintended consequences of immune therapy for immune-mediated diseases: paradoxical psoriasis (PsO) and dupilumab-associated musculoskeletal (MSK) syndrome.

## Unintended consequences of TNFi therapy: Paradoxical PsO, by Dr. Elizabeth Wallace

The development of many novel biologic medications has significantly improved the therapeutic options available to treat psoriatic disease (PsD). One class of biologic medications is TNFi, which were the first commonly used biologics in rheumatology and dermatology.<sup>6</sup> Five TNFi have been approved by the US Food and Drug Administration (FDA), including etanercept, adalimumab, infliximab, certolizumab pegol, and golimumab. All but golimumab are approved for the treatment of PsO. TNFi are also approved to treat other inflammatory and autoimmune conditions. Despite approval of these medicines, treatment with TNFi can lead to development of new or worsening PsD, an unwanted effect termed *paradoxical PsO*.<sup>7</sup> Although all TNFi have the potential to induce paradoxical PsO, infliximab is most commonly associated with this effect.<sup>8</sup> The first cases of paradoxical PsO were published in 2003 in patients with TNFi-treated PsO and ankylosing spondylitis.<sup>9,10</sup> Since then, paradoxical PsO has arisen during TNFi treatment for rheumatoid arthritis, ankylosing spondylitis, inflammatory bowel disease, PsD, and hidradenitis suppurativa, and may affect between 2% and 5% of treated patients.<sup>7,9-14</sup> The estimated time to development of paradoxical PsO varies widely in studies, and differences in onset may vary by the TNFi used.<sup>15,16</sup> It is critical that clinicians are aware of this unintended consequence of therapy so that prompt treatment of the paradoxical PsO can be initiated.

The pathogenesis of paradoxical PsO from TNFi has not yet been fully elucidated. However, several proposed mechanisms exist. One hypothesis implicates an abnormal type I interferon

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(IFN) response. Skin plasmacytoid dendritic cells, a producer of type I IFNs, has been found to play a key initiating role in classic PsO development.<sup>17</sup> TNF normally inhibits plasmacytoid dendritic cell maturation and therefore also prevents type I IFN production from the plasmacytoid dendritic cells.<sup>11</sup> When TNF is blocked by a TNFi, there is an increased and prolonged production of type I IFNs, which is sufficient to induce psoriatic lesions of paradoxical PsO independent of T cells.<sup>18</sup> However, type I IFN production from plasmacytoid dendritic cells may also promote CD8+ T cell migration to the skin, with subsequent development of the cutaneous lesions of PsO.<sup>11</sup>

*Considerations for clinical practice.* The most common presentations of paradoxical PsO include plaque PsO and palmoplantar pustular PsO.<sup>11,16</sup> Affected patients may exhibit multiple PsO subtypes and have many body areas affected, including the scalp and inverse areas such as the axillae or groin.<sup>19</sup> Interestingly, paradoxical PsO may present as psoriasiform dermatitis, a rash with clinical and histologic features of both PsO and eczematous dermatitis.<sup>18</sup> New-onset PsO is more frequently described than exacerbation or recurrence of preexisting PsO or a new PsO morphology in a patient with known PsO. Female patients may be more affected and pediatric patients are also at risk for this adverse effect.<sup>15,16,20</sup>

Distinctive histologic features have been described in paradoxical PsO. The absence of parakeratosis, the presence of neutrophils in the epidermis, and 3 or more dermal eosinophils per histologic section were significantly more likely in paradoxical PsO than in idiopathic PsO. Idiopathic PsO was significantly more likely to present with neutrophils in the stratum corneum and papillary plate thinning.<sup>21</sup> Interestingly, other histopathologic reaction patterns have been seen in lesions of a paradoxical psoriasiform rash, including lichen-planus-like dermatitis and pustular folliculitis as well as the psoriasiform dermatitis described earlier.<sup>18,22</sup> Therefore, a biopsy of a new-onset psoriasiform rash in a patient being treated with a TNFi may help guide the clinician toward a diagnosis of this phenomenon.

Notably, other biologic therapies used to treat PsO have also been implicated in causing paradoxical psoriatic eruption, including the IL-17i secukinumab and ixekizumab, the IL-12/23i ustekinumab, and the IL-23i risankizumab, as well as the IL-4/13i dupilumab, which is used in the treatment of atopic dermatitis.<sup>15,23,24</sup> It is important that clinicians remain on alert for this phenomenon when treating patients with PsO with these medications.

*Management.* An individualized approach to each patient is needed for the management of paradoxical PsO arising from TNFi. Clinicians must consider the severity of paradoxical PsO, determined by factors including the body surface area affected, involvement of any special sensitive sites, and impact on quality of life, to determine the aggressiveness of therapy needed to control the eruption. Clinicians must also consider the degree of control of the underlying condition being treated with the TNFi, meaning that the provider prescribing the medication should be consulted. If the underlying condition is well-managed with the TNFi, changing biologic classes may not be appropriate, particu-

larly when there are few alternative efficacious or FDA-approved treatment options for several of these diseases.

In a mild case of paradoxical PsO with a well-controlled underlying condition, the clinician may first consider implementing a topical PsO treatment regimen. Common first-line topical treatment options for PsO include topical steroids and topical vitamin D analogs. In the case of a recalcitrant mild flare or an initial moderate-to-severe flare of paradoxical PsO with a well-controlled underlying condition, health-care providers could consider topical PsO therapy with the addition of narrowband UVB phototherapy and/or a systemic agent that is compatible with the patient's underlying medical comorbidities, current medications, and social habits. Systemic agents include methotrexate, cyclosporine, and acitretin. These should be prescribed and monitored only by a provider experienced in managing these medications, given their inherent risks as well as additive risks when combined with biologics. In the case of a paradoxical pustular PsO flare, dapsone and acitretin can be helpful adjunct therapies. Further, in a recalcitrant mild case or moderate-to-severe case of paradoxical PsO, switching to another TNFi may be necessary even if the underlying condition is well-controlled. Data suggest that the likelihood of controlling this degree of paradoxical PsO without a change to the underlying trigger (ie, the TNFi) is low.<sup>8</sup>

When a paradoxical PsO flare occurs in cases in which the underlying condition is not well-controlled or the initial trial of switching to another TNFi is not successful, moving to a non-TNFi systemic medication could be considered in conjunction with the typical PsO treatments mentioned above. In this situation, an ideal scenario would be use of an FDA-approved systemic therapy to manage both PsO and the underlying condition. In some cases, treating paradoxical PsO may need to occur in tandem with a change of systemic treatment approved for the underlying condition. For example, both hidradenitis suppurativa and PsO can be treated with the IL-17i secukinumab, whereas inflammatory bowel disease and PsO can be managed with the IL-12/23i ustekinumab. When considering switching medication classes, it is essential that this be a collaborative effort with the patient's healthcare team. Treatment algorithms for paradoxical PsO have been proposed and can be helpful to reference for the dermatologist, rheumatologist, and gastroenterologist.<sup>8,16</sup>

*Conclusion.* Paradoxical PsO induced by TNFi is an unintended consequence of this class of therapy that occurs across many of their indications. Further research is needed to better understand the pathogenic mechanism and to develop an optimal treatment approach. Clinicians, including dermatologists, rheumatologists, and gastroenterologists, need to be aware of this not uncommon phenomenon to be able to identify it and implement a collaborative and individualized therapeutic plan.

**Unintended consequences of therapy: Dupilumab-induced MSK syndrome and paradoxical PsO, by Dr. Bruce Kirkham with Drs. Catherine Hughes and Bina Menon**

*Dupilumab-associated MSK syndrome.* In this section, we discuss an unintended adverse event of direct interest to rheumatolo-

gists and dermatologists, a dupilumab-induced MSK syndrome that is very similar to psoriatic arthritis (PsA).

Dupilumab is a monoclonal antibody that binds the IL-4 $\alpha$  receptor, blocking IL-4 and IL-13.<sup>25</sup> Since these are key pathways for atopic dermatitis (AD), dupilumab was licensed for use in patients with severe AD in 2021 and has also been recently licensed for use in atopic asthma.<sup>26</sup> We first reported that 3 patients with AD receiving dupilumab developed significant arthritis/enthesitis.<sup>27</sup> This initial finding was supported by subsequent case reports from other centers and our updated report.<sup>28,29</sup> We recently described in detail an observational cohort of 26 patients with AD (14 male and 12 female) receiving the licensed dupilumab dose (600 mg loading dose followed by 300 mg every 2 weeks). These patients, seen in our department between October 2018 and February 2021, experienced new-onset MSK symptoms.<sup>30</sup> All patients had a routine comprehensive rheumatological history and examination including the Spondyloarthritis Research Consortium of Canada (SPARCC) enthesitis score, with imaging by ultrasound or magnetic resonance imaging. These 26 subjects presented with an MSK syndrome of inflammatory enthesitis/tenosynovitis/arthritis, with a median onset after 17 (range 2-48) weeks of therapy. Two patients with preceding MSK symptoms had new onset of very different symptoms. Two patients with arthritis had elevated inflammatory markers and 1 patient became positive for antinuclear antibodies. All patients had documented improvement in their AD, with group Eczema Area and Severity Index (EASI) scores having a mean 80% improvement. No predictors of the MSK syndrome were noted. One patient developed guttate PsO and disabling arthritis/enthesitis. Sixteen patients had mild symptoms that responded to nonsteroidal antiinflammatory drugs or COX-2 inhibitor therapy, together with prolongation of dupilumab dosing frequency. Three of 6 patients with moderate and all 4 with severe symptoms stopped dupilumab and changed therapy, but some still experienced prolonged symptoms lasting up to 12 months. Several who switched to Janus kinase inhibitor (JAKi) therapy had improved skin and resolution of MSK symptoms.

Subsequently, we have seen 16 more patients with a similar pattern of MSK symptoms developing after initiation of dupilumab therapy for AD. Half of these patients had imaging, which confirmed the clinical MSK findings. Eight stopped dupilumab therapy, which resulted in the resolution of their MSK symptoms. Of these, 3 successfully restarted dupilumab at a lower dosing frequency, whereas 4 switched to new therapies (1 methotrexate and 3 JAKi). The ongoing presentation of new patients supports our initial reports. In early use, not all patients taking dupilumab were asked routinely about MSK symptoms and the subsequent coronavirus disease 2019 (COVID-19) pandemic made follow-up very difficult.

**Mechanisms.** There are a few studies that may provide insight into the mechanisms underlying the development of an MSK syndrome after treatment with cytokine inhibitors. In an *ex vivo* model using stimulated normal enthesal cells, IL-4, but not IL-13, suppressed IL-23 and subsequent IL-17 production,<sup>31</sup> similar to *in vitro* findings.<sup>32</sup> A potential mechanism of this

adverse event may relate to rapid blockade of high levels of IL-4, and perhaps IL-13, altering enthesal/joint cytokine balance with unopposed basal IL-17/23 and/or TNF expression, activating inflammatory pathways similar to that in PsA. This homeostatic balance of different cytokine pathways in the skin is supported by reports that some patients treated for PsO with IL-17i therapy developed AD-like rashes,<sup>33</sup> which responded to dupilumab in a recent report.<sup>34</sup> The reverse situation also occurs, in which some patients with AD treated with dupilumab develop psoriasiform skin rashes.<sup>35</sup> A nonexclusive alternative mechanism would involve skin-homing T cells, which change after dupilumab therapy<sup>36</sup> and may traffic to enthesal/joint sites. This could explain the prolonged MSK symptoms in some patients after stopping dupilumab.

The frequent presentation of enthesitis strongly supports the theory that potential inflammatory responses to enthesal stress and/or microdamage are actively controlled by immunological mechanisms including cytokines.<sup>37</sup> The extension of dupilumab to atopic asthma and use of other type 2 cytokine pathway inhibitors, such as IL-13 blockers in AD, will most likely extend our understanding of the role that type 2 cytokines play in inflammatory conditions. This will encompass not only different cytokine inhibitors but also the relationship of the MSK system to modifying inflammation at different tissue sites such as the skin and lung.

### Summary and conclusions

Altogether, both presentations at the GRAPPA 2023 annual meeting discussed unintended consequences of treating diseases with TNFi and dupilumab. Both drugs can lead to the eruption of paradoxical PsO and, in the case of dupilumab, can result in an MSK syndrome resembling PsA. Clinicians should be aware of these unintended side effects so that patient-specific coordination of care can occur.

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