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TNF Inhibitor-Induced Psoriasis: Proposed Algorithm for Treatment and Management

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Abstract

Tumor necrosis factor a (TNF-α)-targeted therapies have expanded the therapeutic options for patients with inflammatory bowel disease (IBD), rheumatoid arthritis (RA), psoriasis, and psoriatic arthritis (PsA) and have significantly improved patients' quality of life. Paradoxically, anti-TNF-α agents may induce psoriatic eruptions or worsen preexisting psoriatic skin disease. Currently, there is no standard approach for the management of TNF inhibitor-induced psoriasis. Here, we conduct a literature review on TNF inhibitor-induced psoriasis and introduce a novel treatment algorithm for maintaining otherwise effective anti-TNF therapy versus switching to a different class as appropriate in the management of patients with IBD, RA, psoriasis, or PsA.

Keywords

TNF inhibitor-induced psoriasis; biologic agents; TNF-α

Introduction

There is substantial evidence to support the role of tumor necrosis factor α (TNF-α) in the pathogenesis of several inflammatory conditions which has led to the increased use of TNF-α-targeted therapies to treat inflammatory bowel disease (IBD), rheumatoid arthritis (RA), psoriasis, and psoriatic arthritis (PsA).[1,2] Currently, there are 5 existing TNF-α inhibitors approved by the Food and Drug Administration (FDA): etanercept, infliximab, adalimumab, certolizumab pegol, and golimumab. The development of these biologic drugs expanded the therapeutic options for patients with these conditions and has significantly improved their quality of life.[3–5]

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Declaration of Conflicting Interests

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Paradoxically, anti-TNF-α agents may also induce and/or worsen psoriatic skin lesions in about 0.6% to 5.3% of patients, with Crohn disease and RA being the most common underlying diseases.[6] This cutaneous reaction can be present clinically as plaque psoriasis (15.8%–50%), palmoplantar pustular psoriasis (33.3%–45%), psoriasiform (19.9%), guttate (7%–15%), generalized pustular psoriasis (5.3%–12%), and inverse psoriasis(1.7%–4%).[7–11] Eruptions can also appear on the nails and scalp.[6] Interestingly, patients can exhibit lesions with different morphological features.[12]

The histopathologic features involve a spectrum of cutaneous reactions that include psoriasis-like patterns, eosinophilic hypersensitivity reactions, lichen planus–like dermatitis, or a sterile pustular folliculitis.[12,13] In our experience, aside from the palmoplantar variant, the presentation of a psoriasiform dermatitis with clinical overlapping features of eczematous hypersensitivity and psoriasis (supported by histopathology of a spongiotic psoriasiform dermatitis with eosinophils) is one of the more common presentations suggestive of this entity.[12]

In the current literature, infliximab (52.6%–62.5%) is the most reported TNF-α inhibitor to elicit psoriasiform eruptions; etanercept (12–29%), adalimumab (14.4–34%), certolizumab pegol (1%), and golimumab (0.5%) have also been implicated.[6,7,9,10] Because these lesions have been reported with all TNF-α inhibitor agents, TNF inhibitor-induced psoriasis is suggested to be a class effect.[14]

Currently, there is no standard approach for the management of TNF inhibitor-induced psoriasis. Here, we present a literature review on TNF inhibitor-induced psoriasis and introduce a treatment algorithm for maintaining otherwise effective anti-TNF therapy versus switching to another class as appropriate in the management of patients with IBD, RA, psoriasis, or PsA in the setting of TNF inhibitor-induced psoriasis.

Tumor Necrosis Factor Inhibitor-Induced Psoriasis in Inflammatory Conditions

Rheumatoid Arthritis

The prevalence of psoriasis during anti-TNF treatment in RA is estimated at 2.3% to 5%.[15,16] Data from a large prospective cohort in the United Kingdom evidenced that the incidence rate of psoriasis in patients with RA treated with anti-TNF agents is significantly higher (1.04; 95% confidence interval [CI]: 0.67–1.54 per 1000 person years) compared to patients treated with conventional diseasemodifying antirheumatic drugs (rate of 0; upper 97.5% CI: 0.71 per 1000 person-years) in a 5207 person-years of follow-up. Furthermore, they found that the incidence rate of psoriasis among those treated with adalimumab was significantly higher compared to those treated with etanercept and infliximab[17]; these findings were later supported by Joyau et al.[11] Interestingly, Hernandez et al found a global incident rate of 2.3/1000 patient-years, but subanalysis among different biologic agents does not show significant differences.[18] Overall, patients with RA developing anti TNF-induced psoriasis tended to be females, with no family history of psoriasis, and the median time from initiation of therapy to the onset of psoriasis was about 6 months.[17] Pustular psoriasis was

the phenotype most described followed by plaque psoriasis.[9] Of note, treatment with certolizumab pegol and golimumab has also been associated with anti-TNF-induced psoriasis in RA.[19,20]

Inflammatory Bowel Disease

Although the prevalence of TNF inhibitor-induced psoriasis in IBD is estimated at 1.6% to 2.7%,[21,22] the psoriasis incidence rate is 0.53% per patient year with a cumulative incidence estimated at 1% at year 1, 2.5% at 5 years, and 4.5% at 10 years.[23] Of note, being a smoker or having history of smoking was associated with a higher risk of developing TNF inhibitor-induced psoriasis in several studies.[23] Furthermore, Guerra et al also found that female sex increased the risk of anti-TNF-induced psoriasis in patients with IBD.[23] Although a higher absolute frequency number of cases have been reported among patients treated with infliximab, the incident rate of TNF inhibitor-induced psoriasis was similar for all anti-TNF agents.[23] A possible explanation for the high absolute frequency is that adalimumab was introduced as an IBD therapy later compared to infliximab.[22] In general, patients with IBD presenting with TNF inhibitor-induced psoriasis did not have personal or family history of psoriasis, the median time from initiation of therapy to the development of skin lesions was 12 months (maintenance period), and the most common phenotype of psoriasis was palmoplantar pustulosis.[21–23] Interestingly, in 1 case series of 14 pediatric patients with IBD treated with anti-TNF-α therapy, psoriasis lesions most commonly occurred during IBD remission.[24]

Psoriasis and PsA

Tumor necrosis factor inhibitor-induced psoriasis has also been reported in patients with psoriasis and PsA, though the prevalence of new-onset TNF-induced psoriasis is unclear.[25,26] These paradoxical psoriatic eruptions sometimes manifest in originally unaffected skin, suggesting de novo psoriasis rather than exacerbation of previous lesions.[9,11] Importantly, patients may exhibit a new or different morphology from their original presentation of psoriasis.[6,9] Indeed, patients with a history of plaque or guttate psoriasis may develop pustular lesions after TNF-α inhibitor therapy.[8] Moreover, patients with psoriasis with no history of guttate psoriasis may develop guttate lesions during TNF-α inhibitor therapy.[11] In fact, the prevalence of guttate psoriasis in these patients is estimated at 53% to 78%.[8,9] Paradoxical onset of PsA was also observed by Napolitano et al in a cohort of 327 patients receiving biologic therapy.[26] This study identified 22 cases, of which 18 patients were receiving anti-TNF therapy and 4 were receiving ustekinumab. The majority of the cases presented with peripheral arthritis, with oligoarthritis being the most common presentation.[26] Unlike the cases in RA and IBD, women and men were equally affected in these studies.

Proposed Pathogenesis of TNF-α Inhibitor Induced Psoriasiform Dermatitis

The mechanism of TNF inhibitor-induced psoriasis remains unclear. Several theories have been proposed to explain the etiology of this cutaneous reaction, which are briefly discussed below.

Increased Type 1 Interferon

Classical psoriasis is thought to be initiated by skin plasmacytoid dendritic cells (pDCs), which are normally downregulated by TNF-α.[27] These pDCs produce type 1 interferons (IFNs) which induce the autoimmune response by promoting activation and maturation of conventional dendritic cells that stimulate $CD8^+$ T cells to migrate into the epidermis and promote the growth of psoriatic lesions.[28]Accordingly, one theory regarding the mechanism of TNF-α inhibitor-induced psoriasis hypothesizes that blocking TNF-α allows an increased and uncontrolled production of type 1 IFNs by pDCs, which may induce and/or worsen psoriasiform lesions.[8] Indeed, skin lesions from patients with TNF-α inhibitor-induced psoriasis, when compared to those with classical psoriasis, are characterized by increased levels of type I IFNs and pDC.[29] Furthermore, treatment with IFN-α has been implicated to induce and exacerbate psoriasis.[30]

Interleukin-23/T-helper 17 Axis Theory

The role of interleukin (IL)-23/T-helper (TH)-17 axis has also been implicated in the pathogenesis of TNF inhibitor-induced psoriasis.[9,31–34] Interleukin-23 is a proinflammatory cytokine that promotes TH-17 activation that has been implicated in the pathogenesis of chronic inflammatory diseases such as RA, IBD, and psoriatic disease.[35,36] Interestingly, patients with Crohn disease with TNF inhibitor-induced psoriasis were more likely to be homozygous for polymorphisms in the IL-23 receptor gene compared to disease-matched controls.[32,37] Histological analysis of anti-TNF-induced psoriasis lesions showed an increased number of IFN-y-secreting Th-1 and IL-17-/IL-22- secreting Th17 cells, similar to genuine psoriasis. Accordingly, Tillack et al demonstrated for the first time the efficacy of ustekinumab, an IL-12/23 antagonist, for paradoxical anti-TNF psoriasis. Furthermore, they showed that patients with severe forms of anti-TNF-induced psoriasis requiring ustekinumab presented a higher number of IL-17A-expressing T cells compared to patients not requiring ustekinumab.[32] In short, the emerging evidence for the role of IL-23/TH-17 axis has suggested that this is a new potential target for therapy.

Permissive Infections

Infections are a known trigger for psoriatic lesions.[38] Patients receiving anti-TNF-α therapy have increased risk for infection.[39,40] Accordingly, infection may play a role in the manifestation of TNF inhibitor-induced psoriasis. It has been suggested that exposure to infectious organisms may induce keratoderma blennorhagicum, histologically indistinguishable from pustular psoriasis, which may be the lesions described as TNF inhibitor-induced psoriasis.[41] These palmoplantar psoriasiform lesions have been linked to chlamydial infection, for which TNF-α has been implicated in controlling and limiting.[42]

Already at Risk for Psoriasis

It is well established that patients with chronic rheumatologic and gastrointestinal inflammatory disease such as IBD have higher incidence of psoriasis.[43,44] The prevalence of IBD in patients with psoriasis is estimated to be around 1.4%.[45] In contrast, the prevalence of psoriasis in patients with IBD is approximately 9.6% of patients with Crohn disease and 5.7% of patients with ulcerative colitis.[46,47] Indeed, in a retrospective chart review of

patients with IBD, those with TNF-α inhibitor-induced psoriasiform eruptions had a greater genetic predisposition for psoriasis compared to patients who did not develop psoriasis while receiving TNF-α inhibitor therapy.[48] Thus, patients who have a history of these diseases may be predisposed to TNF inhibitor-induced psoriasis.

Treatment of Anti-TNF-Induced Psoriasis

The treatment of TNF-inhibitor-induced psoriasis is challenging. The decision to continue, suspend, or replace the anti-TNF therapy has to be carefully discussed with the patient considering the severity of the skin eruption, the needs of the underlying disease, and the availability of other treatment options. Of note, the severity of skin eruption should be defined considering the extent of the psoriatic eruption (eg, body surface area) as well as its impact on the quality of life of the patient (eg, involvement of palms, soles, face, genitals, and psychological impact) as recommended by the National Psoriasis Foundation.[49] Thus, in this review, we will define mild psoriatic eruption as those cases in which both the extension of the disease and the impact on quality of life are considered tolerable by the patient, and moderate to severe otherwise. Here, we propose an algorithm illustrating different options for the treatment of TNF inhibitor-induced psoriasis in Figure 1.

Mild Skin Eruption

Controlled underlying disease.—In the setting of mild TNF inhibitor-induced psoriasis and when a patient's underlying disease state is otherwise well managed on current anti-TNF therapy, a "treat-through" approach with typical therapies for psoriasis may be the most prudent. The psoriasis therapies to be considered include topical steroids, UV therapy, methotrexate, cyclosporine (although not favored long-term therapy option), or acitretin, as appropriate. Notably, we consider cyclosporine with some caution in combination with other biologics, as this therapy is typically used only for short-term bridge therapy when necessary and not as a long-term agent. Indeed, adverse events with administration of concomitant anti-TNF agents and cyclosporine in patients with severe IBD, most notably infections and at least 2 deaths,[50,51] have been reported in the literature.

This "treat through" strategy has demonstrated complete resolution in 26% to 41% of the cases and a partial response in 25% to 57.4% (Table 1).[7–10] Historically, "treating through" TNF inhibitor-induced psoriasis has been important for patients with IBD given the evidence that discontinuation of biological therapy can aggravate gastrointestinal symptoms and the limited therapeutic class options.[52]

Pustular psoriasis, which is one of the most frequently observed clinical presentation of anti-TNF induced psoriasis, can be treated with dapsone or acitretin. Dapsone is an "anti-neutrophil" agent that has been shown to improve pustular psoriasis in patients who had previously failed several topical and systemic therapies.[53] Of note, dapsone has fewer side effects than other systemic therapies.[54] Furthermore, topical dapsone 5% gel has a safe side effect profile given its low systemic absorption.[55] In addition to dapsone, clinicians can also consider acitretin, an oral retinoid used as the first-line therapy to treat generalized pustular psoriasis.[56] Indeed, there has been one case report of ustekinumab-induced pustular

psoriasis that resolved after acitretin treatment, with no recurrence of these lesions at the patient's 6-month follow-up.[57]

Uncontrolled underlying disease.—When patients present with mild TNF inhibitor-induced psoriasis and the underlying disease state is not well controlled, we propose switching to a different anti-TNF agent while maintaining psoriasis-specific therapy. However, the rate of success of this approach is limited since complete resolution was only observed in 5% to 36.7% of cases, with partial response in 18.4% (Table 1).[6–9]

Moderate to Severe Skin Eruption

Controlled underlying disease.—When patients have moderate to severe skin eruption and their underlying disease is well controlled, switching to a different anti-TNF agent can be considered. As cited before, complete regression of psoriasis lesion was seen in only 5% to 36.7% of cases (Table 1).[6–9]

Uncontrolled underlying disease and refractory cases.—For patients with moderate to severe anti-TNF-induced psoriasis whose underlying disease is active despite anti-TNF-therapy and refractory cases, agents outside the anti-TNF class should be considered, combined with topical or systemic therapy for psoriasis as appropriate. Indeed, it has been reported that in up to approximately 64.3% of cases, patients who discontinue TNF inhibitors and switch to therapies outside the TNF class experience resolution of their psoriasiform lesions.[6] Below, we discuss different alternative therapies for RA, IBD, psoriasis, and PsA. An overview of these agents is presented in Table 2.

Rheumatoid Arthritis

Non-anti-TNF biologic agents have been demonstrated to be, in some cases, as or more effective treatment compared to a second anti-TNF drug for patients with RA with insufficient primary response to anti-TNF-α inhibitor, suggesting the need for a different mechanism of action.[96] Indeed, tocilizumab, rituximab, abatacept, and tofacitinib have been significantly more effective in treating RA when compared to placebo in these patients.[97] Importantly, abatacept and tofacitinib are an FDA-approved drugs for PsA.

Inflammatory Bowel Disease

Although TNF-α inhibitors have improved clinical outcomes for patients with IBD, many patients fail to attain remission with anti-TNF-α therapy.[98] For this patient population that have failed TNF-inhibitor therapy, we recommend ustekinumab specifically in the setting of Crohn disease or vedolizumab as viable treatment options for patients with IBD. Notably, both ustekinumab and vedolizumab seem to have the same response and remission rate in patients with Crohn disease who failed prior TNF-α inhibitor therapy.[99] Of note, substantial evidence supports the long-term efficacy and safety of ustekinumab in the treatment of psoriasis in both clinical trials and clinical settings.[100] Accordingly, Guerra et al reported 8 cases of TNF-induced psoriasis cases treated with ustekinumab, of which 75% experienced complete resolution.[23] Furthermore, Pugliese et al achieved complete clearance of skin lesions in all 3 cases treated with ustekinumab.[101]

Additionally, we also recommend discussions with IBD-treating physician or gastroenterology regarding traditional IBD treatments such as immunosuppressive agents including 6-mercaptopurine and azathioprine versus newer biologic therapies.

Psoriasis and PsA

Several treatment options are available for patients with psoriasis and PsA who failed TNF-α inhibitor therapy. Guselkumab is a viable treatment option for patients with psoriasis, while ustekinumab, ixekizumab, secukinumab, and apremilast have demonstrated efficiency in treating patients with both psoriasis and PsA. Finally, tofacitinib and abatacept are viable treatment options for patients with PsA only.

Discussion

Tumor necrosis factor inhibitor-induced psoriasis is not uncommon. This cutaneous reaction can manifest in several forms including plaque psoriasis, palmoplantar pustular psoriasis, psoriasiform, guttate, and inverse psoriasis.[11] Growing evidence supports the notion that paradoxical psoriasis is a class effect.[6,7] The increasing incidence of TNF-α induced psoriasis in a crowded landscape of therapeutic options supports the need for algorithmic guidance to treat TNF inhibitor-induced psoriasis. Here, we propose an algorithm from a dermatologic standpoint in which the severity of the skin eruption and the characteristics of the underlying disease guide the medical decision. In contrast, previously published algorithms in the rheumatologic literature founded their treatment choices exclusively on the severity of skin disease.[8] Taken together, our algorithm outlines specific therapies for each underlying disease, including the most recently approved agents by the FDA.

Our algorithm proposes that for those cases with mild induced psoriasis in patients whose underlying disease is well controlled, a “treat through” approach with traditional therapies for psoriasis is the preferred option. Conversely, for those patients with mild skin eruption and uncontrolled underlying disease or patients with moderate-to-severe induced psoriasis with good control of underlying disease, temporal withdrawal of anti-TNF therapy or switching to other anti-TNF agents could be considered. However, it is important to acknowledge that more than half of the patients may experience recurrence of skin lesions after the reintroduction of either the same or a different anti-TNF.[23,102,103] Thus, for refractory cases of induced psoriasis as well as for patients with moderate to severe skin eruption whose underlying disease is not well controlled, our algorithm emphasizes switching the drug class to increase the likelihood of resolution of the paradoxical psoriasis.

Understanding the inflammatory pathways involved in the onset of this adverse event and that of the underlying disease is of paramount importance to select the most appropriate treatment for patients who have failed or are otherwise intolerant to anti-TNF-α agents. Indeed, the identification of the role of the IL-23/Th-17 axis in paradoxical psoriasis has become critical in the management of these cases. For example, ustekinumab is an anti-IL12/23 agent that had led to resolution of skin lesions in more than 75% of the cases in patients with IBD.[32,104,105] Likewise, the efficacy of anti-IL17 agents in genuine psoriasis and PsA suggests anti-IL17 agents as another promising class of agents for paradoxical psoriasis. Of note, anti-IL17 agents should be used with caution in patients with both

psoriasis and IBD, since there is evidence that they may exacerbate or induce IBD in patients with psoriatic disease.[106]

Despite the advances in the pathogenesis of paradoxical psoriasis, significant gaps remain as this cutaneous reaction has also been described for some of the alternative therapies described in this review. Indeed, paradoxical psoriasis and PsA have been described in patients treated with ustekinumab.[105] Then rituximab has been associated with de novo and flare of existing psoriasis in patients with seronegative RA and systemic lupus erythematosus.[107,108] Similarly, new onset of psoriasis and exacerbation of previous psoriasis were observed in a few patients with RA and PsA treated with abatacept.[109,110] Finally, 2 cases of de novo psoriasis were described in patients with RA treated with tocilizumab.[111,112]

Other indications of anti-TNF agents include uveitis, ankylosing spondylitis, and juvenile RA. As paradoxical psoriasis in these conditions has been less frequently reported compared to RA, psoriatic disease, and IBD, we did not include them in our discussion.

Conclusion

Tumor necrosis factor inhibitor-induced psoriasis is not uncommon and has been observed to be a class effect. Here, we propose a novel algorithm that incorporates new treatment options for patients with RA, IBD, psoriasis, and PsA with TNF inhibitor-induced psoriasis and highlights the strategy to switch therapy outside the TNF class when clinically appropriate. Because paradoxical psoriasis has also been described for some of these classes of drugs, further studies are required to better characterize the safety and efficacy of this approach. Thus, we recommend discussing these treatment options in a case-by-case basis and incorporating multidisciplinary care physicians for treating the underlying disease.

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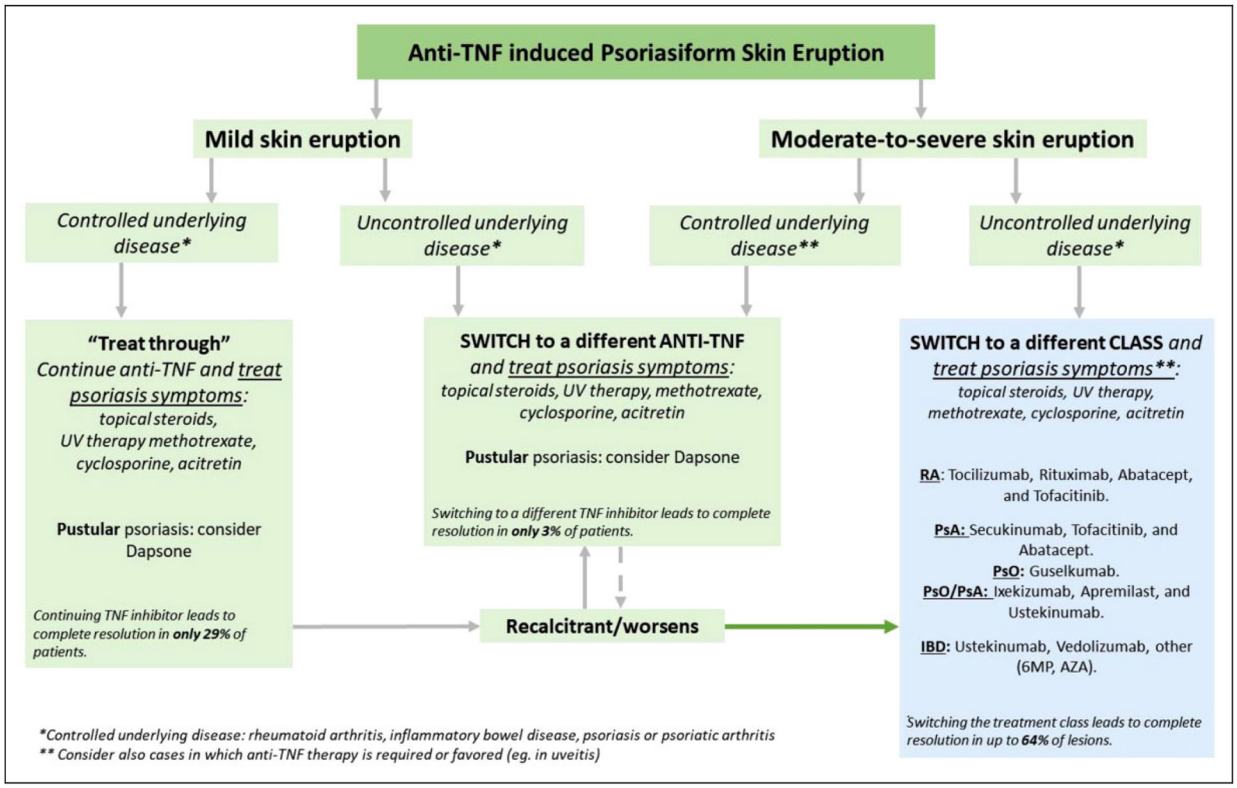

Figure 1.

Upon the onset of anti-TNF-induced psoriasiform skin disease, the severity of the skin eruption and the efficacy of the anti-TNF drug on the underlying primary disease (RA, IBD, psoriasis, and PsA). For those patients with mild psoriasiform disease and stable underlying disease, we propose a "treat through" strategy in which the anti-TNF therapy will be continued and conventional psoriasis-specific therapy will be added (eg, topical steroids, UV therapy, methotrexate, cyclosporine, and acitretin). If the skin eruption is recalcitrant or worsens, or if the primary condition is poorly controlled, we propose switching to another anti-TNF or to another class. For patients with moderate to severe skin eruption and stable underlying disease, we propose switching to a different anti-TNF and treat the psoriasis symptoms concomitantly. If this fails, a different class should be considered. Instead, for those cases in which the underlying disease is not well controlled with an anti-TNF, we suggest switching to another class. *Controlled underlying disease: rheumatoid arthritis, inflammatory bowel disease, psoriasis, or psoriatic arthritis. **Consider also cases in which anti-TNF therapy is required or favored as in uveitis. IBD indicates inflammatory bowel disease; PsA, psoriatic arthritis; RA, rheumatoid arthritis; TNF, tumor necrosis factor.

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Table 1.

Summary of Clinical Outcomes per Treatment Modality for Anti-TNF-Induced Psoriasis Across Multiple Underlying Diseases Reported in the Literature.

	Ko et al, 2009[6] (N = 127)	**Collamer et al,[8] 2008 (N= 114)**	**Collamer et al,[9] 2010 (n = 207)**	**Brown et al,[7] 2017 (N =216)**	**Schmidt etal,[10] 2012 (N = 56)**
Continued on TNF therapy				N =82	N =22
Resolved, n (%)		31 (30)	53 (26)	27 (32.9)	9(41)
Improved, n (%)		32(31)	52 (25)	47 (57.4)	8(36)
No improvement, n (%)		2(2)	2(1)	8 (9.8)	5(23)
Partial or no resolution combined					
Discontinued off TNF therapy				N =65	N =21
Resolved, n (%)		14 (13%)	50 (24)	31 (47.7)	12(57)
Improved, n (%)				30 (46.2)	4(19)
No improvement, n (%)				4 (6.2)	1 (5)
Partial or no resolution combined		4(4)	11 (5)		
Switched to different TNF agent	N = 13			N =49	
Resolved/no recurrence at follow-up, n (%)	2(15.4)	5(5)	13(6)	18 (36.7)	
Improved, n (%)				9 (18.4)	
No improvement, n (%)				22 (44.9)	
Resolved off anti-TNF and recurred with a different anti-TNF		8(8)	12(6)		

Abbreviation: TNF, tumor necrosis factor.

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Table 2.

Summary of Therapy Options for Patients With RA, IBD, Psoriasis, and PsA With TNF Inhibitor-Induced Psoriasis.

Drug/Brand Name	Mechanism of Action	FDA-Approved Indication(s) of Relevance	Special Considerations
RA			
Tocilizumab/Actemra	Anti-IL-6 monoclonal antibody	RA	Tocilizumab has demonstrated to be a viable treatment option for patients with RA who have failed TNF-a inhibitor therapy.[58] Of note, tocilizumab may be more effective when combined with methotrexate than when used as monotherapy.[59,60]
Rituximab/Rituxan	Anti-CD20 monoclonal antibody	RA	Patients with RA who previously failed TNF inhibitor therapy who switched to rituximab saw significant improvement in their RA compared to those who switched therapy to a second TNF inhibitor.[61] This effect was particularly striking in seropositive patients. Other studies have demonstrated similar results.[62,63]
Abatacept/Orencia	Selective T-cell costimulation blocker	RA	Abatacept is a viable treatment option for patients with moderate to severe RA who failed one or more TNF-a inhibitor therapies or disease-modifying antirheumatic drugs (DMARDs). Patients with active RA who failed prior TNF-a inhibitor therapy showed significantly more improvement in physical function when treated with abatacept for 6 months.[64] Notably, clinicians should discontinue etanercept treatment before treating with abatacept, as an increase in serious adverse events was observed when these 2 therapies were used in combination.[65]
Tofacitinib/Xeljanz	Janus-associated kinase QAK) inhibitor	RA PsA	Tofacitinib is a treatment option for patients with RA and demonstrated to have similar efficiency to adalimumab in treating RA.[66] Additionally, tofacitinib used in combination with methotrexate improved RA in patients who failed prior TNF-a inhibitor therapy.[67,68]
IBD			
Ustekinumab/Stelara	Anti-IL-12 and anti-IL-23 monoclonal antibody	Moderate to severe plaque psoriasis PsA Crohn disease	Patients with Crohn disease who have failed anti-TNF-a agents have reported resolution of psoriatic lesions after treatment with ustekinumab.[69,70] Moreover, in a cohort of anti-TNF resistant patients with Crohn disease, 73.7% of patients responded to subcutaneous ustekinumab.[71] Ustekinumab therapy has also significantly improved TNF inhibitor-induced palmoplantar pustulosis in a patient with a history of Crohn disease.[72]
Vedolizumab/Entyvio	a4|37 Integrin antagonist monoclonal antibody	Crohn disease and ulcerative colitis	Vedolizumab is a treatment option for patients who failed prior conventional treatment of TNF-a inhibitor therapy.[73,74] Of note, patients with IBD who primarily received vedolizumab had higher rates of response and remission than those who were treated with anti-TNF-a agents in the past, though previous treatment to anti-TNF-a agents does not significantly affect vedolizumab efficacy.[75,76]
Psoriasis/PsA			
Secukinumab/Cosentyx	Anti-IL-I7A monoclonal antibody	Moderate to severe plaque psoriasis PsA	Secukinumab is a treatment option for moderate to severe plaque psoriasis and PsA that can effectively treat patients with PsA who failed prior TNF-a therapy.[77,78] In a recent systematic review comparing the effectiveness of several treatments for PsA, secukinumab was found to be the most effective in treating PsA in both the anti-TNF-a-naive and anti-TNF-a-experienced cohorts.[79] Furthermore, patients with PsA who have previously been treated with ustekinumab seem to have a greater response to secukinumab.[80]

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Drug/Brand Name	Mechanism of Action	FDA-Approved Indication(s) of Relevance	Special Considerations
Ixekizumab/Taltz	Anti-IL-17 A monoclonal antibody	Moderate to severe plaque psoriasis PsA	Ixekizumab is a treatment option for adult moderate to severe psoriasis. There are limited data regarding the efficiency of ixekizumab in treating patients with psoriatic disease who failed TNF-a inhibitors, 1 study demonstrated improved signs and symptoms after 24 weeks of treatment with ixekizumab in patients with PsA who failed prior anti-TNF-a therapy.[81] Of note, in the UNCOVER trials, patients with moderate to severe plaque psoriasis exhibited greater responses to ixekizumab therapy compared to etanercept and placebo.[82]
Apremilast/Otezla	Phosphodiesterase-4-inhibitor	Moderate to severe plaque psoriasis PsA	Apremilast is a treatment option for moderate to severe plaque psoriasis and PsA. Although there are limited data on the efficiency of apremilast in treating psoriasis or PsA in patients who failed TNF-a inhibitors, apremilast has been demonstrated to be effective and safe in treating patients with active PsA who were treated with DMARDs or biologies in the past.[83] The safety and efficacy of switching from etanercept to apremilast in treating psoriasis is supported in the LIBERATE study.[84]
Ustekinumab/Stelara	Anti-IL-12 and anti-IL-23 monoclonal antibody	Moderate to severe plaque psoriasis PsA Crohn disease	Ustekinumab is a treatment option for moderate to severe psoriasis and PsA, which can efficiently treat TNF inhibitor-induced psoriasis.[85] Two case reports saw resolution of psoriasiform eruptions secondary to adalimumab in females with PsA treated with ustekinumab every 3 months.[86] Furthermore, ustekinumab has also been implicated in successfully treating 4 cases of recalcitrant palmoplantar pustulosis, one of which was anti-TNF inhibitor induced.[87] Interestingly, there has been 1 case report of a 30-year-old male who previously failed infliximab therapy whose psoriasis was exacerbated after treatment with ustekinumab.[88]
Abatacept/Orencia	Selective T-cell costimulation blocker	RA	Abatacept is a treatment option for PsA used where other drugs have failed. Several studies support the efficacy of abatacept in treating patients with PsA who have failed prior anti-TNF therapy, particularly in improving musculoskeletal manifestations of PsA.[89,90]
Tofacitinib/Xeljanz	Janus-associated kinase QAK) inhibitor	RA PsA	Tofacitinib is a treatment option for patients with PsA that has been shown to reduce disease activity in patients with PsA who failed prior TNF inhibitor therapy.[91] Additionally, tofacitinib has also been shown to effectively treat patients with PsA with previous inadequate response to conventional synthetic DMARDs.[92] Notably, tofacitinib is not FDA approved to treat psoriasis.
Guselkumab/Tremfya	Anti-IL-23 monoclonal antibody	Moderate to severe plaque psoriasis	Guselkumab is a treatment option for moderate to severe psoriasis that has demonstrated superior efficacy compared to adalimumab for treating psoriasis.[93,94] Importantly, guselkumab has been shown to be effective in treating patients with psoriasis who had failed prior anti-TNF therapy.[95]

Abbreviations: FDA, Food and Drug Administration; IBD, inflammatory bowel disease; IL, interleukin; PsA, psoriatic arthritis; RA, rheumatoid arthritis; TNF, tumor necrosis factor.