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Permalink
https://escholarship.org/uc/item/3jt91556

Journal
Dermatology Online Journal, 27(11)

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Publication Date
2021

DOI
10.5070/D3271156085

Peer reviewed

Off-label uses of TNFα inhibitors and IL12/23 inhibitors in dermatology

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Abstract

TNFα inhibitors, which include adalimumab, infliximab, etanercept, certolizumab, and golimumab, and IL12/23 inhibitor, ustekinumab, have been widely used as a U.S. Food and Drug Administration (FDA) approved for the treatment of psoriasis. Outside of psoriasis, high levels of TNFα had also been found in several skin diseases including hidradenitis suppurativa. IL12 and IL23 play important role in the pathogenesis of SLE, alopecia areata, and vitiligo. This paper reviews the off-label uses of TNFα inhibitors and IL12/23 inhibitors in skin disorders.

Keywords: adalimumab, certolizumab, etanercept, golimumab, hidradenitis suppurativa, infliximab, TNFα, ustekinumab

Introduction

In the past two decades, there have been new developments in many highly efficacious biologic therapies for the treatment of psoriasis and psoriatic arthritis. Tumor necrosis factor-alpha (TNFα) is a proinflammatory cytokine that affects immune responses in both dermatologic and systemic diseases [1]. TNFα inhibitors including adalimumab, infliximab, etanercept, certolizumab pegol, and golimumab have been shown to be safe and effective in the treatment of psoriasis in several phase III randomized clinical trials. Ustekinumab is a human monoclonal antibody that blocks the interleukin (IL)-12/23 receptor, which inhibits further downstream inflammatory cascade. It is Food and Drug Administration (FDA) approved to treat psoriasis, psoriatic arthritis, and inflammatory bowel disease (IBD), including Crohn's disease and ulcerative colitis (UC), [2].

Off-label uses of psoriasis treatments have been considered for recalcitrant dermatologic conditions that do not respond to conventional systemic therapies. Often, these diseases show overlaps in their pathogenesis: TNFα inhibitors act on Th1 pathways and IL12/23 inhibitors act on both the Th1 and Th17 pathways. These shared pathogenic pathways lead to a broad potential of these biologic therapies in non-approved, inflammatory skin diseases. In this review, we evaluate the efficacy and safety of TNFα inhibitors and IL12/23 inhibitors for off-label indications in non-psoriatic dermatological diseases.

Methods

A literature search was performed using the MEDLINE (PubMed) was conducted in May 2021 using the search terms: dermatology treatment AND (((ustekinumab) NOT psoriasis) OR ((etanercept) NOT psoriasis) OR ((infliximab) NOT psoriasis) OR ((certolizumab) NOT psoriasis) OR ((golimumab) NOT psoriasis) OR ((adalimumab) NOT (psoriasis or hidradenitis suppurativa))). One reviewer identified all included articles (JH). Only studies written in the English language were reviewed. Clinical trials and nonexperimental descriptive studies, such as case series and case reports, were chosen for the purpose

of this paper. Inclusion criteria were articles on treatment of non-approved dermatologic conditions with TNFα inhibitors and IL12/23 inhibitors and were published prior to April 2021. Exclusion criteria were articles on treatment of approved dermatologic conditions or non-dermatologic conditions and the use of therapy other than TNFα inhibitors and IL12/23 inhibitors.

Results

A total of 901 papers that were unique and relevant to our search was identified. After applying the inclusion and exclusion criteria, 144 unique papers were chosen for the purpose of our review. Thirty-seven papers on clinical studies and 107 papers on case reports and case series were reported. Twenty-seven papers on adalimumab, 57 papers on infliximab, 29 papers on etanercept, two papers on certolizumab pegol, two papers on golimumab, and 27 papers on ustekinumab were reviewed. In **Table 1**, we have summarized our results by grading our findings by evidence levels based on the best available evidence. Grade 1A indicates that there is evidence from meta-analysis of randomized controlled trials. Grade 1B indicates that there is evidence from at least one randomized controlled trial. Grade 2 indicates that there is evidence from at least one controlled study without randomization. Grade 3 indicates that there is evidence from case reports, case series, and other types of non-experimental study. For the purpose of our review, we have summarized the findings from clinical trials and indicated whether case reports have found the biologics to be safe and effective.

Hidradenitis suppurativa (HS)
The first randomized clinical trial of the use of infliximab in the treatment of moderate-to-severe HS showed a significant difference between the infliximab group (60%) and the placebo group (5.6%) with a 25-50% decrease in HS Severity Index score (HSSI) after 22 weeks of treatment dosed every eight weeks [3]. Patients treated with placebo showed less than 25% decrease from baseline HSSI (88.9%). Furthermore, infliximab treatment resulted in significant clinical improvement in Dermatology Life

Quality Index score (DLQI), Physician Global Assessment (PGA), pain, visual analog scale score, and other biomarkers of inflammation, such as ESR and CRP.

A more recent clinical trial of 42 patients treated with higher doses of infliximab showed significant decrease in PGA from the baseline scores [4]. Twenty out of forty-two (47.6%) patients achieved clinical responses at week 4 with infliximab 7.5mg/kg every four weeks. 17/24 (70.8%) patients achieved clinical responses at week 12 with infliximab 10mg/kg every four weeks (P<0.001). At week 4, 24/42 (57.1%) patients and 19/24 (79.2%) patients had a HS-PGA score of 0 to 2 at weeks 4 and 12, respectively. From week 0 to week 4, there was a significant decrease in Numerical Rating Scale (NRS) for pain scores (P<0.001) and the results were sustained through week 12 (P<0.001). No adverse event was reported throughout the trial. Our search resulted in four case reports have also reported on the efficacy and safety of infliximab for the treatment of HS [5–8].

An open-label phase II study treated 10 HS patients with etanercept 50mg once weekly for 12 weeks [9]. At week 12, there was greater than 50% improvement in their disease activity and Sartorius score as well as self-reported visual analogue scale (VAS) and DLQI. 1 patient presented with an abscess in the right gluteal area after 6 weeks of etanercept discontinuation. However, a phase II clinical trial of etanercept 50mg once weekly in HS patients reported that only 3/15 patients who entered the study were categorized as responders with response rate of 20% based on the intention-to-treat analysis [10]. Two patients withdrew from the study because of skin infections at the site of HS lesions. Another randomized prospective study found that etanercept 50mg twice weekly for 12 weeks did not result in statistically significant difference in PGA and DLQI between treatment and placebo groups [11].

An open-label clinical trial studying ustekinumab in HS found that improvement of modified Sartorius scale (mSS) was achieved in 15/17 (88.2%) patients [12]. Improvement of modified Hidradenitis Suppurativa Lesional Area Severity Index (mHSLASI) was achieved in 12/17 (70.6%) patients at week 40. Ustekinumab was well tolerated in these patients

with no serious adverse event reported. Our search resulted in two case reports of severe HS successfully treated with high-dose ustekinumab [13,14].

Pyoderma gangrenosum (PG)
In a retrospective cohort study, 52 patients with PG who have failed to improve with corticosteroids (92.3%) or cyclosporine A (51.9%) were treated with TNFα inhibitors, ustekinumab, or intravenous immunoglobulins (IVIGs), [15]. Complete remission of PG or marked improvement was shown in 21/33 (63.6%) patients on infliximab, 16/28 (57.1%) patients on adalimumab, 5/7 (71.4%) patients on etanercept, 6/9 (66.6%) patients on ustekinumab, and 10/15 (66.7%) patients on IVIG. These therapies were overall more effective than treatment with corticosteroids (38/78; 48.8%) or cyclosporine A (7/35; 7.0%). Three case reports have shown the efficacy of ustekinumab in recalcitrant PG with complete resolution at an average of 12 weeks of treatment [16–18].

In a randomized clinical trial, 30 patients with PG were randomized to receive infliximab (N=13) or placebo (N=17), [19]. At the end of week 2, 6/13 (46%) patients treated with infliximab showed clinical improvement (determined by PGA), which was significantly superior to 1/17 (6%; P=0.025) in the placebo group. By the end of week 6 of treatment, in 23 of the patients who were offered open label infliximab after failure to improve by week 2, 69% (N=20) showed clinical improvement with 21% (N=6) demonstrating complete remission.

Our search resulted in several case reports on the successful treatment of PG with adalimumab [20–25], infliximab [20,22,26–36], etanercept [37,38], certolizumab pegol [39,40], golimumab [41], and ustekinumab [16–18].

Systemic lupus erythematosus (SLE)
There are two phase II randomized clinical trials that investigated the efficacy and safety of ustekinumab in patients with active SLE [42,43]. In the first study, 102 patients were randomly assigned to receive ustekinumab (N=60) or placebo (N=42), [42]. Their primary endpoint was the proportion of patients achieving a systemic lupus erythematosus disease activity index 2000 (SLEDAI-2K) responder index-4

(SRI-4) response at week 24. Systemic lupus erythematosus responder index-4 encompassed combinations of factors including the location of the lesions and race and gender of the patients. At the end of the treatment, 37/60 (62%) patients in the ustekinumab group achieved an SRI-4 response, compared to 14/42 (33%) patients in the placebo group (P=0.006). Infections accounted for approximately half of the recorded adverse events (48/102), and there was no death, malignancy, or treatment-emergent opportunistic infections, such as herpes zoster or tuberculosis that occurred during the treatment.

The second study evaluated the maintenance of the efficacy and safety of ustekinumab in SLE patients [43]. The study found that the patients treated with ustekinumab who had achieved SRI-4 at week 24 maintained the response through week 48 (63.3%). Adverse events reported through week 56 remained consistent with those reported at week 24 in the earlier study. 15.1% in the ustekinumab group reported serious adverse events throughout the 56 weeks. These results indicated that ustekinumab treatment is a safe and effective treatment for SLE with long-lasting response and offers an alternative to long-term glucocorticoid use. There is one case report on the successful treatment of SLE with infliximab [44].

Atopic dermatitis (AD)
One open-label, prospective study evaluated the long-term efficacy and safety of infliximab in nine patients with moderate-to-severe AD [45]. Patients were given infliximab 5mg/kg at week 0, 2, and 6 for their induction therapy, and then they were given the same dose at week 14, 22, 30, and 38 for maintenance therapy. Infliximab monotherapy resulted in more than 50% improvement in the mean eczema area and severity index (EASI) from 22.5 at week 0 to 10.6 at week 2. Pruritus severity assessment (PSA) decreased from 2.8 at week 0 to 1.4 at week 2. Six patients withdrew from the study due to low EASI improvement <30% at weeks 10, 14, and 30. Three patients reported headache or nausea, which were classified as mild adverse events. One patient withdrew at week 10 due to a serious infusion reaction causing temporary flush and

dyspnea. The adverse reaction resolved upon discontinuation of the infusion.

A randomized, placebo-controlled, phase II study conducted in Japan showed that ustekinumab did not show efficacy in patients with severe AD [46]. 79 patients were randomized to receive either ustekinumab 45mg (N=24), 90mg (N=28), or placebo (N=27) for 12 weeks. At week 12, the mean changes from baseline EASI score were -38.2% (P=0.94) for ustekinumab 45mg group, -39.8% (P=0.81) for ustekinumab 90mg group, and -37.5% for placebo group. There were 18/24 (75%) patients with treatment-emergent adverse events in ustekinumab 45mg group, 16/28 (57%) patients in the 90mg group, and 20/27 (74%) patients in the placebo group. The most frequent adverse events observed were nasopharyngitis and worsening of AD.

A case series on the treatment of severe AD with ustekinumab in 10 patients showed that four patients (40%) responded to treatment [47]. The injection doses were either 45mg or 90mg at weeks 0, 4, and every 12 weeks thereafter. The mean duration of treatment was 19.2 months (range: 4-71). One patient developed an elevated alanine transferase, and no other adverse effects were reported.

Pemphigus vulgaris (PV)
In a randomized clinical trial, 20 patients received either infliximab or placebo in addition to topical prednisone at weeks 0, 2, 6, and 14 to investigate possible efficacy and safety of infliximab for the treatment of pemphigus vulgaris [48]. One out of ten (10%; 90% CI: 0.1-0.39) patients responded to infliximab at week 18 compared to 1/10 (10%; 90% CI: 0.1-0.39) placebo patients. 3/10 (30%; 90% CI: 0.09-0.61) patients on infliximab at week 26 compared to 0/10 (0%; 90% CI: 0-0.26) placebo patients. 5/10 (50%) patients on infliximab achieved cessation of new blisters compared 3/10 (30%) placebo patients. There was no significant difference in the number of treatment-related adverse events between the two study arms.

A pilot study in 2011 evaluated the efficacy and safety of etanercept for PV treatment in eight patients [49]. Subjects were randomized (2:1) to receive etanercept 50mg or placebo injections once weekly for 16 weeks. Two patients in the etanercept group withdrew from the study due to PV flare at week 4 for first patient and hip fracture at week 8 for the second patient. 2/6 (33.3%) patients in the placebo group and 1/6 (16.7%) in the etanercept group achieved 50% reduction in lesion number. Three subjects failed etanercept treatment, but one showed clinical improvement with smaller lesions and less erythema. There was no other severe adverse event that was reported.

Granuloma annulare
A case series in 2016 evaluated the efficacy of adalimumab in treating seven adults with generalized or disseminated granuloma annulare (GA). End points included improvements in GA Investigator Global Assessment score, body surface area, erythema, and induration. All patients achieved a two point or greater improvement in GA investigator global assessment score. Average improvements in body surface area, erythema, and induration were 87%, 88%, and 95%, respectively [50]. Two adverse events were reported, one patient was diagnosed with alopecia areata and another patient experienced loss of energy. Multiple case reports have evaluated the efficacy of adalimumab in patients with GA [51,52]. Similarly, case reports have also measured the therapeutic benefit of infliximab in patients with GA [53–55].

Alopecia areata
A prospective, open-label pilot study evaluated the efficacy of etanercept in 17 patients with moderate to severe alopecia areata, alopecia totalis, or alopecia universalis [56]. The main study assessment included improvements in the Severity of Alopecia Tool (SALT) score. Of the patients that completed the 24-week treatment period of the study, none of the patients experienced an improvement in their SALT score by more than 10% of their baseline score, with some patients experiencing worsening of disease. Common adverse events included injection site reaction, fatigue, and upper respiratory infection. There are two case reports evaluate the efficacy and safety of ustekinumab in alopecia areata [57,58].

Cutaneous sarcoidosis

A prospective, open-label, randomized, 12-week study evaluated the use of adalimumab in patients presenting with cutaneous sarcoidosis. Ten patients were randomized to receive adalimumab and 6 patients were randomized to receive placebo. Efficacy measurements included improvements in the Physician Global Assessment (PGA) of the overall volume of cutaneous lesions, area of target lesion selected at baseline, volume of the target lesion, and DLQI score. The study reported improvements in target lesion area, volume, and Dermatology Life Quality Index Score [59]. The most common reported adverse events were headache, musculoskeletal symptoms, pulmonary symptoms, infections, and gastrointestinal symptoms. Case reports have also reported efficacious results of infliximab in treating patients with cutaneous sarcoidosis [60–63].

Severe cutaneous adverse reactions (SCARS)

In a randomized trial with 96 patients presenting with Stevens-Johnson syndrome (SJS) and toxic epidermal necrolysis (TEN), the efficacy of etanercept was compared to traditional corticosteroids. Assessments included the score of toxic epidermal necrolysis (SCORTEN) and time to complete skin-healing. Etanercept showed superior improvements in SCORTEN-based predicted mortality rate and skin-healing time compared to corticosteroids. With regard to safety assessments, a lower incidence of gastrointestinal hemorrhage was also noted.[64] Multiple case reports have also discussed the benefit of etanercept in patients with SJS-TEN. Infliximab has also been evaluated as a therapeutic option for patients presenting SJS-TEN, though studies have been limited to case reports on infliximab [65–68] and etanercept [69–75].

Other dermatologic diseases

There are case reports on the efficacy and safety of TNFα inhibitors and IL12/23 inhibitor for the treatment of the following skin diseases: cheilitis granulomatosa [76,77], erythema nodosum leprosum [78–82], chilblain lupus [83], sporadic blau syndrome [84–86], acne fulminans [87,88], PASH syndrome [89], necrobiosis lipoidica [90–97], PAPA syndrome [98], dermatomyositis [99], chronic spontaneous urticaria [100], lichen planus pemphigoides [101], autosomal recessive congenital ichthyosis [102], acne conglobate [8,103,104], impetigo herpeiformis [105], melanoma [106], actinic granuloma [107], pityriasis rubra pilaris [108–124], acrodermatitis continua of Hallopeau [125–128], Sweet syndrome [129,130], Sneddon-Wilkinson disease [131,132], acute generalized exanthematous pustulosis [133], chronic lichen sclerosis [134], generalized morphea [135], lupus pernio [136], and vitiligo [137].

Discussion

There are many clinical trials and case reports that suggest that TNFα inhibitors and IL12/23 inhibitors may be potential off-label treatments for several dermatological diseases. The shared pathogenesis between psoriasis and these diseases can play in important role in treatment efficacy of these biologics. Specifically, infliximab had been used as a potential treatment for HS, PG, SLE, AD, GA, PV, cutaneous sarcoidosis, SCARS, and many other skin conditions. While clinical trials have been conducted in diseases, other diseases that are mentioned in this article have been used in case reports and case series.

In our search, there was a limited number of clinical trials that studied the efficacy and safety of TNFα inhibitors and IL12/23 in non-approved skin diseases. Our search resulted in both clinical trials and case reports in the use of these biologic drugs in HS, PG, SLE, AD, granuloma annulare, PV, cutaneous sarcoidosis, alopecia areata, and SCARS (**Table 1**). There are only case reports on the use of certolizumab pegol in PG and golimumab in PG and chilblain lupus. There is paucity of data on certolizumab pegol and golimumab because they obtained FDA approval only recently in 2018 and 2020, respectively. Certolizumab is also indicated for adult patients with active psoriatic arthritis, but not psoriasis which could discourage the use of this drug for the treatment of skin conditions.

TNFα inhibitors may be effective in treating certain skin diseases because of their shared pathophysiology with psoriasis. For example, the inflammatory role of TNFα in HS was discovered

when TNFα inhibitors were used to treat patients with inflammatory bowel disease (IBD) with concomitant HS, which improved significantly with their IBD treatment [138]. Studies have also found that HS patients had higher concentrations of TNFα in their serum and skin lesions compared to healthy volunteers [138,139]. Currently, adalimumab is an FDA-approved treatment for moderate-to-severe HS [140]. This suggests that targeting TNFα can curtail immune response that leads to clinical improvement.

IL12 and IL-23 also play important role in pathophysiology of SLE, alopecia areata, and vitiligo, suggesting a potential novel therapy in targeting these cytokines [141]. IL12 and IL-23 play important roles in driving the Th17>Th1 pathway, suggesting that ustekinumab may present as a potential therapy for both alopecia areata and vitiligo [142]. Several reports of hair regrowth in patients with alopecia areata and depigmentation in patients with vitiligo after treatment with ustekinumab have been published [57,58,143]. Both TNFα inhibitors and ustekinumab have shown efficacy in neutrophilic dermatoses including PG when corticosteroids and cyclosporine do not yield desirable treatment outcome.

Conclusion

The current literature has indicated that TNFα inhibitors show potential in treating HS, PG, and SCARS, and IL12/23 inhibitors show potential in treating SLE and pityriasis rubra pilaris. Many case reports have also shown the efficacy and safety of these biologic therapies in treating non-approved skin conditions. More data from clinical studies are needed to further evaluate these drugs for off-label uses.

Potential conflicts of interest

The authors declare no conflicts of interest.

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Table 1. *Off-label dermatologic uses of TNFα inhibitors and IL12/23 inhibitors categorized by level of evidence.*

Skin Condition	TNFα inhibitors					IL12/23 inhibitors	References
	Adalimumab (N=27)	Infliximab (N=57)	Etanercept (N=29)	Certolizumab (N=2)	Golimumab (N=2)	Ustekinumab (N=27)	
Acne conglobata (N=3)	3		3				[8,103,104]
Acne fulminans (N=2)	3						[87,88]
Acrodermatitis continua of Hallopeau (N=4)	3		3			3	[125–128]
Actinic granuloma (N=1)	3						[107]
Acute generalized exanthematous pustulosis (N=1)			3				[133]
Alopecia areata (N=3)			2			3	[56-58]
Atopic dermatitis (N=3)		2				1B	[45-47]
Autosomal recessive congenital ichthyosis (N=1)						3	[102]
Chelitis granulomatosa (N=2)		3					[76,77]
Chilblain lupus (N=1)					3		[83]
Chronic lichen sclerosis (N=1)	3						[134]
Chronic spontaneous urticaria (N=1)			3				[100]
Cutaneous sarcoidosis (N=5)	1B	3					[59-63]
Cytotoxic T lymphocyte-mediated severe cutaneous adverse reactions: SJS, TEN (N=12)		3	1B				[64-75]
Dermatomyositis (N=1)		3					[99]
Erythema nodosum leprosum (N=6)		3	3				[78–82]
Generalized morphea (N=1)		3					[135]
Granuloma annulare (N=6)	3	3					[50-55]
Hidradenitis suppurativa (N=12)	FDA-approved	1A	1A			2	[4–14]
Impetigo herpetiformis (N=1)	3						[105]
Lichen planus pemphigoides (N=1)						3	[101]
Lupus pernio (N=1)		3					[136]
Melanoma (N=1)	3						[106]
Necrobiosis lipoidica (N=8)	3	3	3			3	[90–97]
Pemphigus vulgaris (N=2)		1B	1B				[48, 49]
Pityriasis rubra pilaris (N=19)	3	3	3			3	[108–124]
Pyoderma gangrenosum (N=32)	1B	1A	2	3	3	2	[15-41]

Pyoderma gangrenosum, acne, and hidradenitis suppurative syndrome (N=1)		3					[89]
Pyogenic arthritis, pyoderma gangrenosum, and acne syndrome (N=1)	3						[98]
Sneddon-Wilkinson disease (N=2)		3	3				[131,132]
Sporadic blau syndrome (N=3)	3	3					[84–86]
Sweet syndrome (N=2)	3						[129,130]
Systemic lupus erythematosus (N=3)		3				1A	[42-44]
Vitiligo (N=1)		3					[137]

Grade 1A indicates that there is evidence from meta-analysis of randomized controlled trials. Grade 1B indicates that there is evidence from at least one randomized controlled trial. Grade 2 indicates that there is evidence from at least one controlled study without randomization. Grade 3 indicates that there is evidence from case reports, case series, and other types of non-experimental study.