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REVIEW

Novel and Off-Label Biologic Use in the Management of Hidradenitis Suppurativa, Pyoderma Gangrenosum, Lichen Planus, and Seborrheic Dermatitis: A Narrative Review

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ABSTRACT

With advances in drug development and our understanding of the pathophysiology of skin disease, biologic medications have emerged as powerful management tools for dermatologists. While biologics have most often been used in the management of psoriasis, they are being used off-label for the management of a variety of other immune-mediated skin diseases with overlapping molecular targets. This narrative review focuses on the novel and off-label use of biologic medications for the management of hidradenitis suppurativa (HS), pyoderma gangrenosum (PG), lichen planus (LP), and seborrheic dermatitis (SD). Review of the literature revealed that IL-17, IL-23, and tumor necrosis factor (TNF) inhibitors were being used across a variety of immune-mediated skin pathologies with variable efficacy, among other targeted biologics. While biologics were generally safe in the treatment of primary immune-mediated skin disorders, paradoxical disease eruptions were noted with biologic use and were theorized to occur owing to immune dysregulation and cytokine imbalance. While numerous case reports show promise for the use of biologics in immune-mediated skin pathologies, the variable efficacy and safety reported warrants more thorough investigations of the role of these targeted medications in comprehensive disease management.

Keywords: Biologics; Off-label; Treatment; Hidradenitis suppurativa; Pyoderma gangrenosum; Lichen planus; Seborrheic dermatitis

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Key Summary Points

Biologic agents are being used off-label in the management of a variety of immune-mediated skin conditions including hidradenitis suppurativa (HS), pyoderma gangrenosum (PG), lichen planus (LP), and seborrheic dermatitis (SD).

Reports of off-label IL-17 and IL-23 inhibitor use were common for HS, PG, and LP, however evidence was variable and paradoxical eruptions were also reported.

Other biologics such as dupilumab, rituximab, tumor necrosis factor (TNF) inhibitors were also reported in both management and paradoxical eruption of these conditions.

Paradoxical SD reactions were reported with dupilumab use, however evidence for off-label biologic use for management of SD was not detected in our literature review.

Evidence detected in this review was primarily through case reports and series, and further studies are required to properly assess the role of novel biologic agents in the management of HS, PG, LP, and SD.

INTRODUCTION

With advances in the understanding of the pathophysiology of skin disease, biologic therapies have emerged as powerful management tools for a variety of inflammatory skin conditions. Often favored owing to contemporary studies [1] demonstrating safety and efficacy, a potential lower side effect profile, and more rapid resolution when compared with broad immune suppression, biologic therapies have gained favor with many dermatologists for the management of recalcitrant and treatment-resistant immune-mediated skin disease. Biologic agents have been used most extensively in the management of psoriasis [2]; however, off-label use has been documented in the literature for a variety of other autoimmune skin conditions with overlapping molecular targets. In this narrative review we sought to characterize the off-label use of these biologic medications in the management of hidradenitis suppurativa (HS), pyoderma gangrenosum (PG), lichen planus (LP), and seborrheic dermatitis (SD).

METHODS

A literature review was performed for the most recent case reports and interventional studies of biologic use in the management of hidradenitis suppurativa (HS), pyoderma gangrenosum (PG), lichen planus (LP), and seborrheic dermatitis (SD). The authors searched the PubMed database for studies in English, and articles published between 2012 and 2022 were considered for this review. The articles considered in this review are summarized in Table 1. This was not a systematic review, and results may not be directly comparable owing to differences in methodology, endpoints, and objectives. The purpose of this review is to characterize the existing literature supporting off-label use of biologics for the management of immune-mediated skin disease. This article is based on previously conducted studies and does not contain any new studies with human participants or animals performed by any of the authors.

HIDRADENITIS SUPPURATIVA

Hidradenitis suppurativa (HS) is a chronic inflammatory disorder characterized by nodules, abscesses, fistulae, sinus tracts, and scars typically affecting intertriginous cutaneous regions such as the axilla, inguinal, submammary, and perianal areas. HS lesion formation occurs secondary to follicular hyperkeratosis and inflammation in the pilosebaceous apocrine glands, and current treatment guidelines

Table 1 Articles reviewed for off-label use of biologics in the management of hidradenitis suppurativa, pyoderma gangrenosum, lichen planus, and seborrheic dermatitis

Disease	Agent	Target	Studies reviewed
Hidradenitis suppurativa	Ixekizumab	IL-17	Reardon et al. 2021 [4], Megna et al. 2020 [5], Iannone et al. 2021 [6], Odorici et al. 2020 [7], Gordon et al. 2014 [8], Pirro et al. 2019 [9]
	Secukinumab	IL-17	Casseres et al. 2020 [10], Schuch et al. 2018 [11], Kimball et al. 2022 [12], Babino et al. 2022 [13]
	Risankizumab-rzaa	IL-23	Caposiena et al. 2021 [14], Flora et al. 2021 [15], Marques et al. 2021 [16]
	Tildrakizumab-asmn	IL-23	Kok et al. 2021 [17], Kok et al. 2020 [18]
	Guselkumab	IL-23	Janssen Research & Development LLC 2021 [19], Casseres et al. 2019 [20], Kearney et al. 2020 [21], Jørgensen et al. 2020 [22], Agud-Dios et al. 2022 [23], Croitoru et al. 2022 [24], Garcia-Melendo et al. 2020 [25], Melgosa Ramos et al. 2022 [26]
	Ustekinumab	IL-23	Montero-Vilchez et al. 2022 [27], Jiang et al. 2022 [28], Hollywood et al. 2022 [29]
	Dupilumab	IL-4Rα	Kaakati et al. 2021 [30], Gambardella et al. 2020 [31], Molinelli et al. 2022 [32]
	Anakinra	IL-1R	Tzanetakou et al. 2016 [33], Zarchi et al. 2013 [34], Menis et al. 2015 [35], Russo et al. 2016 [36], André et al. 2019 [37], Leslie et al. 2014 [38]
Pyoderma gangrenosum	Ixekizumab	IL-17	Kao et al. 2022 [45], Gul et al. 2020 [46], Pollack et al. 2021 [47]
	Secukinumab	IL-17	McPhie et al. 2020 [48], Coe et al. 2022 [49], Li et al. 2022 [50], Nikolakis et al. 2021 [51], Toussi et al. 2020 [52], Moreno García et al. 2019 [53], Jin et al. 2019 [54], Pinard et al. 2018 [55], Wollina et al. 2020 [56]
	Risankizumab-rzaa	IL-23	Weigelt et al. 2021 [57], Burgdorf et al. 2020 [58], Orita et al. 2022 [59]
	Tildrakizumab-asmn	IL-23	John et al. 2020 [60], Kok et al. 2020 [61]
	Guselkumab	IL-23	Reese et al. 2022 [62], Baier et al. 2021 [63]
	Dupilumab	IL-4Rα	Nasseh et al. 2022 [64]

Table 1 continued

Disease	Agent	Target	Studies reviewed
Lichen planus	Secukinumab	IL-17	Solimani et al. 2019 [65], Rezzag-Mahcene et al. 2021 [66], Maglie et al. 2018 [67], Komori et al. 2017 [68]
	Brodalumab	IL-17	Maurelli et al. 2020 [69]
	Tildrakizumab-asmn	IL-23	Kherlopian et al. 2022 [70], Kherlopian et al. 2021 [71], Ismail et al. 2020 [72], Trindade de Carvalho et al. 2020 [73], Kerkemeyer et al. 2020 [74]
	Guselkumab	IL-23	Solimani et al. 2019 [65]
	Ustekinumab	IL-23	Knisley et al. 2017 [75], Webster et al. 2015 [76]
	Etanercept	TNF	Niebel et al. 2020 [77], Yarom et al. 2007 [78]
	Adalimumab	TNF	Holló et al. 2012 [79], Kreutzer et al. 2014 [80]
	Rituximab	CD20	Brennan et al. 2020 [81], Heelan et al. 2015 [82], Tétu et al. 2018 [83]
	Dupilumab	IL-4Rα	Pousti et al. 2021 [84]
	Omalizumab	IgE	Kemeriz et al. 2020 [85], Seeborg et al. 2009 [86]
Seborrheic dermatitis	Dupilumab	IL-4Rα	Al-Janabi et al. 2020 [87], Lukac et al. 2022 [88]

focus on immunosuppression and are stratified by severity.

For management of acute flares, refractory nodules, and sinus tracts, intralesional corticosteroid injections are recommended as monotherapy or adjunct to systemic therapies. Systemic therapies for HS include oral tetracyclines as first-line therapy, a combination regimen of clindamycin and rifampin as second-line therapy, and dapsone or metronidazole/moxifloxacin/rifampin triple therapy as third-line therapy.

Tumor necrosis factor (TNF) and interleukin-17 have been identified as key cytokines in the pathogenesis of HS, and serum levels have been correlated with disease severity [3]. Adalimumab, an anti-TNF antibody and first line biologic agent, is the only biologic currently approved for HS management, however literature review found numerous successful reports of other biologics being used in the management of HS. Infliximab was not included in this review, as despite the absence of regulatory approvals, it is often used as the standard of care for many patients with severe hidradenitis suppurativa. IL-17 and IL-23 inhibitors were used with variable efficacy for the treatment of HS, among other targeted biologics.

IL-17 Inhibitor Use in Hidradenitis Suppurativa

Ixekizumab is a monoclonal antibody inhibitor of interleukin-17 (IL-17), and is currently FDA approved for treatment of psoriasis and psoriatic arthritis. A case report of a 30-year-old female patient with severe HS showed significant improvement after 13 months of subcutaneous ixekizumab therapy following failure of antibiotics, surgery, radiation, and other biologics such as ustekinumab, adalimumab, and infliximab [4]. Similarly, several other case reports corroborate improvement of HS with ixekizumab treatment as short as 4 weeks after treatment initiation [5–7]. Notably, none of these patients experienced adverse effects from ixekizumab therapy. [4–7]

Importantly, there are reports of paradoxical HS exacerbations in patients treated with

biologics for other conditions. In a randomized, placebo-controlled phase 2 trial of ixekizumab in chronic plaque psoriasis, one patient reported several paradoxical HS exacerbations after treatment [8]. Similar paradoxical HS reactions following 12 weeks of ixekizumab therapy for psoriasis have been documented in case reports. [9]

Secukinumab, an IL-17a inhibitor indicated for treatment of psoriasis, ankylosing spondylitis, and psoriatic arthritis, was also identified as a biologic in the treatment of HS. An open-label clinical trial of 14 patients with hidradenitis suppurativa reported a 50% decrease in the total number of abscesses and inflammatory nodules relative to baseline after 24 weeks of secukinumab treatment [10]. Similarly, a case of a 24-year-old patient with a 6-year history of HS reported near complete resolution of inflammatory nodules after 8 weeks of secukinumab treatment [11]. While the full manuscript has not been published, phase 3 studies using secukinumab for HS have shown promising safety and efficacy results, supporting future regulatory approvals of secukinumab for management of HS. [12]

Paradoxical exacerbations of HS were also reported with secukinumab use, and reports of non-response were common. A case of a 47-year-old female patient with psoriasis and psoriatic arthritis treated with secukinumab reported development of Hurley stage II HS after 24 weeks of treatment. Secukinumab was discontinued and adalimumab was started, which improved the HS lesions after 12 weeks. [13] Several additional reports detail secukinumab discontinuation owing to no response following 8–12 weeks of treatment. [10]

IL-23 Inhibitor Use in Hidradenitis Suppurativa

Risankizumab-rzaa, a monoclonal antibody inhibitor of IL-23, is approved for treatment of Crohn's disease and psoriasis. A case report of a 39-year-old female with severe HS showed significant clinical improvement after treatment with risankizumab-rzaa following failure of antibiotics, isotretinoin, surgery, and other biologics such as adalimumab and secukinumab [14]. Several other case reports corroborate these findings with complete resolution and stability of HS skin lesions after treatment with risankizumab-rzaa. A case report of a 29-year-old female patient with severe HS and concomitant synovitis, acne pustulosis, hyperostosis, and osteitis (SAPHO syndrome) treated with risankizumab-rzaa showed reduction in joint and skin pain and drainage from HS lesions as early as week 4 [15]. Notable adverse effects such as tonsillitis have been reported. [16]

Review of the literature also revealed reports of tildrakizumab-asmn use in the management of HS. Tildrakizumab-asmn is a monoclonal antibody inhibitor of IL-23, and is currently approved for the treatment of moderate-to-severe psoriasis. A cohort study of nine patients with severe HS treated with high-dose tildrakizumab reported statistically significant reduction in mean abscess and nodule count at months 2 and 5 ($p = 0.003$). Two patients had flares of HS at month 8 following 50% dose reduction of tildrakizumab [17]. The results of this cohort study are corroborated by a case series of five patients with moderate-to-severe HS and improvement in abscess and nodule count at week 8 compared with baseline, with a mean reduction of 16.8 ($p = 0.04$). Additionally, several patients reported measurable quality-of-life improvement via the Dermatology Life Quality Index (DLQI) and reduction in pain symptoms via the visual analog pain scale (VAS) at week 8 compared with baseline, although the difference did not reach statistical significance (DLQI, mean difference = 8.0; $p = 0.46$; VAS, mean difference = 1.2, $p = 0.64$) [18]. Notably, concomitant antibiotics and surgical management during both study periods may partially contribute to the reported efficacy of tildrakizumab-asmn for HS management [17, 18]. In the literature reviewed, no adverse events were reported with tildrakizumab-asmn use.

Guselkumab, an IL-23 inhibitor approved for treatment of psoriasis and psoriatic arthritis, was also identified as a novel biologic being studied for HS management. A phase 2, double-blind, randomized, placebo-controlled clinical trial of guselkumab in treatment of HS reported significant improvement of patient-reported

outcome measured by DLQI, but failed to achieve Hidradenitis Suppurativa Clinical Response (HiSCR), defined as at least a 50% reduction in total abscess and nodule count, with no increase in abscess count, and no increase in draining fistula count relative to baseline. In the treatment arm, 30 patients (n = 59) achieved HiSCR at weeks 12–16, while 24 patients in the placebo (n = 62) achieved HiSCR; however, there were no significant differences in HiSCR between placebo and treatment groups (19). The efficacy of guselkumab for HS management remains controversial owing to incongruent reports of subjective and objective treatment measures. Additionally, there are reports of guselkumab discontinuation owing to failure of HS lesion response despite intensification of guselkumab dosage [20]. In contrast, several case reports reported significant improvement in severe HS Hurley stages II/III with guselkumab treatment as early as week 12 [21]. Reports of patients with concomitant Crohn's disease have also shown significant improvement of HS with guselkumab therapy [22–24]. Adverse events reported with guselkumab use included sacroiliitis [25] and severe infection [26]; however, these were rare in the literature.

Ustekinumab, a monoclonal antibody targeting both IL-17 and IL-23, is approved for treatment of Crohn's disease, ulcerative colitis, plaque psoriasis, and psoriatic arthritis. Various literature reports identify ustekinumab as an efficacious treatment for HS, particularly in patients with failure to respond to first-line treatments. A case series of ten patients reported a reduction of at least 1 point in the HS Physician Global Assessment (PGA) in seven (70%) patients, and a reduction of ≥ 2 points in Numeric Pain Rating Scale (NPRS) in eight (80%) patients after a median treatment duration of 48 (32–167) weeks. Notably, all patients included in the case series had previously undergone treatment for HS, nine (90%) had received biological therapy with adalimumab or infliximab, and one patient was biologic–naïve. No ustekinumab-related adverse events were reported in any patients [27]. Similarly, a case series of six patients with Hurley stage III HS and failure of adalimumab and infliximab therapy reported a mean percentage change in the International Hidradenitis Suppurativa Score system (IHS4) of −36.1% (95% CI 70.9% to −1.3%), which parallels to reduction in draining fistulae, abscess, and inflammatory nodule count, at weeks 8–12 compared with baseline. Notably, concomitant antibiotic therapy during the study duration may have contributed to the reported efficacy of ustekinumab for HS management [28]. The results of these case series suggest ustekinumab may be an effective and safe option for patients with HS who fail to respond to first-line therapies. Conversely, a retrospective study of 16 patients with moderate-to-severe HS reported variable response to ustekinumab therapy. All patients had failed first-line antibiotic and biologic treatment options. The mean duration of treatment was 16 months and clinical improvement, defined as reduced flare count and improvement in patient quality of life (QoL), was seen in nine (56%) patients. No clinical improvement was documented in four (25%). Three (19%) patients with coexisting Crohn's disease reported good control of HS. Notably, adverse effects, such as recurrent infections, led to treatment withdrawal in one patient [29]. Overall, ustekinumab may be an effective and safe option for patients with refractory HS and HS concomitant with Crohn's disease, albeit variable reports of efficacy.

Other Biologic Use in Hidradenitis Suppurativa

Biologics not directly targeting IL-17 and IL-23 were also identified in the literature as potential therapeutics for the management of HS. HS and atopic dermatitis (AD) are both chronic inflammatory skin diseases and previous studies have found patients with a diagnosis of AD have 5.57-fold increased odds ratio (OR) of having HS as compared with those who do not have AD [30]. This correlation between AD and HS may indicate dupilumab efficacy for treatment of patients with concomitant disease. As such, dupilumab, a monoclonal antibody targeting the IL-4a receptor currently approved for treatment of moderate-to-severe AD, was used

efficaciously in numerous case reports of patients with HS and concomitant AD. One case reported ≥ 50% reduction in HS inflammatory lesion count and no increase in abscesses or draining fistulas compared with baseline after 4 months of dupilumab treatment [31]. Another case of a patient with frequent HS exacerbation and failure of systemic antibiotics reported no HS and AD exacerbation during 6 months of dupilumab treatment [32].

Anakinra, a recombinant IL-1 receptor antagonist approved for treatment of rheumatoid arthritis, was also identified in the literature as a potential HS therapeutic, albeit with variable reports of efficacy. A double-blind, randomized, placebo-controlled clinical trial reported decreased disease activity score in 20% (2 of 10) of the placebo arm compared with 78% (7 of 9) of the anakinra arm ($p = 0.02$). Additionally, HS clinical response at 12 weeks was achieved in 30% (3 of 10) of the placebo arm and 78% (7 of 9) of the anakinra arm ($p = 0.04$). The benefit of anakinra treatment was prolonged, with significantly longer time to new exacerbations of HS during the 12-week follow-up period [33]. The results of this clinical trial suggesting anakinra's potential as an effective treatment for HS are corroborated by several case reports of significant reduction in pain, suppuration, and malodor within 8 weeks of anakinra treatment [34]. Notably, efficacy of anakinra therapy for HS management is inconsistent in the literature. Several case reports found moderate-to-severe HS refractory to 12 weeks of anakinra treatment [35, 36] or loss of anakinra efficacy after several years of treatment [37]. Additionally, an open-label study reported rebound HS following anakinra cessation after initial reduction in HS disease activity [38]. No serious adverse events were recorded in the treatment phase or follow-up phase of the clinical trial [33]; however, anakinra discontinuation due to diarrhea, vaginal candidiasis, and injection site swelling or pain has been reported [33, 36, 37].

Summary of Biologic Use in Hidradenitis Suppurativa

Numerous reports of novel and off-label biologic use in the management of HS were detected in the literature. In particular, IL-17 blocking agents including ixekizumab and secukinumab, and IL-23 blocking agents including risankizumab-rzaa, tildrakizumab-asmn, and guselkumab, seemed of particular interest among clinicians, likely owing to their direct effects on the HS cytokine signature. Paradoxical HS eruptions were reported with IL-17 inhibitors, and clinicians should consider this possibility if these agents are used for treatment of psoriasis. IL-23 inhibitors showed variable efficacy when used in the management of HS, and infections were reported as side effects of treatment. Dupilumab may offer potential benefits when used in patients with coexisting atopic dermatitis, however, further work must be done to understand the relationship between these inflammatory pathologies. A clinical trial of anakinra showed promise in management of HS, however conflicting reports in literature warrant further examination of long-term efficacy of this treatment. A variety of therapeutic targets and promising off-label uses of biologics were noted in the literature for management of HS, and further work must be done to assess the efficacy and safety of these novel treatments to understand their role in comprehensive HS management.

PYODERMA GANGRENOSUM

Pyoderma gangrenosum (PG) is an inflammatory, noninfectious, ulcerative neutrophilic dermatosis that classically affects the extensor surfaces of the legs. PG typically presents in the classic ulcerative form as a painful ulcer with purulent-based and violaceous-undermined border. While PG can occur independently, it is often associated with a causative comorbidity

such as inflammatory bowel disease, hematologic malignancy, or arthritis, and these diseases have an impact on the outcomes [39, 40].

First-line treatments for mild disease include local high-potency steroids or tacrolimus, but many patients require systemic corticosteroids or cyclosporine in addition to aggressive wound therapy. In refractory cases, anti-TNF biologic agents have demonstrated success, in addition to dapsone and minocycline. Although many patients experience remission within 1 year, relapses and complications are common.

IL-17 and IL-23 have been implicated in the pathogenesis of PG, however, a variety of other cytokine targets are still being actively investigated [41]. Currently, no treatments have been approved in the USA for PG; however, adalimumab has been approved for treatment of PG in Japan. Given that adalimumab and infliximab are already strongly evidenced based in the USA, they were not discussed here [42–44]. Review of the literature revealed numerous reports of IL-17 and IL-23 inhibitors being used with variable efficacy to treat PG, among other targeted biologics.

IL-17 Inhibitor Use in Pyoderma Gangrenosum

As with HS, literature review revealed ixekizumab and secukinumab were being used off-label in the management of PG. In one case report, ixekizumab was used successfully to treat cabozantinib-induced PG in a patient with active renal cell carcinoma in whom traditional immunosuppressants were to be avoided [45]. Ixekizumab was also used successfully in one case report to treat PASH syndrome refractory to adalimumab and ustekinumab, with no active lesions present after 12 weeks of therapy [46]. Importantly, as with HS, paradoxical PG presentation after ixekizumab therapy was also reported in the literature. In one patient, vaginal PG developed after ixekizumab therapy, and was only responsive to adalimumab therapy after failing cyclosporine. [47]

Evidence for secukinumab use in PG was conflicting, and while successful remission was achieved in some studies, reports of partial and nonresponse were detected, in addition to paradoxical PG eruptions from secukinumab use. In one report, secukinumab was used to successfully treat PG in a patient with highly recalcitrant disease, with full closure achieved in 3 months with no recurrence [48]. In another report, secukinumab was used to successfully treat a patient with recalcitrant PG, and corresponded with a decrease in DLQI score from 24/30 to 3/30. Importantly, in this patient minimal improvement was seen at a four-weekly dosing, and significant improvement was only seen after dosing was increased to twice weekly [49]. Several reports also detailed success with secukinumab in treating various PG phenotypes, including PASS syndrome [50] and PsAPSASH syndrome [51]. Evidence for secukinumab was conflicting, however, and reports of partial response were detected [52, 53]. In these studies, secukinumab was used after failure of traditional therapies, indicating it still may have a role in comprehensive PG management.

Paradoxical PG eruptions from secukinumab use were also detected in the literature. In one report, a patient who had switched from adalimumab to secukinumab for management of psoriasis developed PG after initiating treatment. In this patient, discontinuation of secukinumab and initiation of cyclosporine therapy resulted in improvement in psoriasis and PG symptoms [54]. This was corroborated by another report of a patient with chronic lymphocytic leukemia and psoriasis who also developed PG after switching therapy from adalimumab to secukinumab. Full resolution was eventually achieved in this patient after treatment with infliximab and methotrexate [55]. A final report also detailed PG eruption after treatment of psoriasis with secukinumab.

These lesions resolved quickly after discontinuation of secukinumab and treatment with pantoprazole, wound care, and systemic and topical steroids [56].

IL-23 Inhibitor Use in Pyoderma Gangrenosum

The literature also reinforced risankizumab-rzaa, tildrakizumab-asmn, and guselkumab use for PG. Risankizumab-rzaa was used successfully in three case reports with few side effects and no paradoxical reactions. In one patient with peristomal PG refractory to cyclosporine, clinical remission was achieved within 3 weeks after a single dose of risankizumab-rzaa [57]. In another patient with highly recalcitrant PG, remission was achieved within four doses despite the simultaneous discontinuation of all other immunosuppressive medications [58]. In another case report, risankizumab-rzaa was successfully used to treat secukinumab-induced PG with additional resolution of existing psoriasis vulgaris [59].

The literature reviewed revealed two reports of successful tildrakizumab-asmn use for the management of PG. In one patient, tildrakizumab-asmn was used successfully in the resolution of long-standing recalcitrant PG as well as in inducing remission of coexisting polymyalgia rheumatica. This was theorized to occur owing to tildrakizumab-asmn's effect on the IL-23/IL-17 cascade, as IL-17 is heavily implicated in polymyalgia rheumatica pathogenesis [60]. A second report detailed successful treatment of PASH syndrome with tildrakizumab-asmn, with a reduction of abscess and nodule count from 45 to 6 a total of 2 months after commencing treatment. Importantly, while abscess and nodule count reduced markedly at 2 months, VAS and DLQI remained high (VAS 9, DLQI 13) [61].

Guselkumab was also reported in the literature for successful resolution of PG in two separate reports of recalcitrant disease. In one patient, complete healing was achieved after four doses in two separate ulcers. Importantly, dosing was adjusted in this patient to an off-label dosing structure [62]. In another report from literature, guselkumab was used to successfully resolve PG refractory to ustekinumab, adalimumab, and infliximab. Re-epithelialization of 95% of the ulcer was achieved within 3 months, and continued remission was noted at 15 months [63].

Other Biologic Use in Pyoderma Gangrenosum

Unlike the success seen with dupilumab use in HS, there were no reports of successful dupilumab use for the management of PG. Review of the literature did reveal one report of paradoxical dupilumab-induced PG in one patient with severe AD and concomitant Crohn's disease. In this patient, wound closure was achieved after discontinuation of dupilumab and treatment with topical steroids and wound care [64].

Summary of Biologic Use in Pyoderma Gangrenosum

Review of the literature revealed numerous reports of off-label and novel biologic use for the management of PG. In particular, IL-17 inhibitors including ixekizumab and secukinumab, and IL-23 inhibitors including risankizumab-rzaa, tildrakizumab-asmn, and guselkumab, had prevalence in review of the literature for off-label PG treatment. Evidence for IL-17 inhibitors was conflicting, as in some cases successful treatment was achieved; however, reports of partial response and paradoxical PG eruptions were also noted. Evidence for IL-23 inhibition was more robust, with multiple reports of successful resolution of various PG phenotypes with off-label biologic treatment. Dupilumab was reported to induce a paradoxical PG reaction in one patient, and clinicians should be aware of this possibility when treating patients. A variety of biologic treatments show promise in management of PG; however, further studies must be done to understand the safety and efficacy of these treatments as paradoxical reactions may occur.

LICHEN PLANUS

Lichen Planus (LP) is an inflammatory skin disorder with a relatively heterogeneous presentation. LP may affect the skin (cutaneous LP), oral mucosa (oral LP), scalp (lichen planopilaris), genitalia (vulvar or penile LP), or nails, and presents with a variety of clinical features depending on the affected area. Cutaneous disease is typically characterized by pruritic, purple, polygonal papules or plaques, and oral disease often features papular, atrophic, or erosive mucosal lesions.

Data supporting evidence-based treatment of LP are lacking, however, the mainstay of treatment includes topical or oral steroids as first-line treatment. Phototherapy and acitretin may be used for steroid refractory cutaneous LP, and calcineurin inhibitors may be used for recalcitrant oral LP.

LP is thought to be mediated by a cytotoxic CD8+ T-cell response, and a number of inflammatory chemokines have been identified as potential therapeutic targets. In particular, increased expression of IL-17 and IL-23 have been noted in LP, and may offer support for use of existing biologics targeting these cytokines. A review of the literature identified numerous reports of off-label use of IL-17, IL-23, and TNF inhibitors in management of LP, among other biologics.

IL-17 Inhibitor Use in Lichen Planus

A review of the literature revealed reports of secukinumab and brodalumab used successfully for the management of a variety of LP morphologies; however, paradoxical LP eruptions after secukinumab treatment were also reported. A cohort study of three patients with mucocutaneous LP demonstrated rapid clinical improvement after treatment with secukinumab, with clinical improvement supported by decreases in ABSIS Skin and Mucosa I scores. Histopathological evidence was also supportive, showing marked reduction of CD4+ and CD8+ T-cell infiltrate in LP lesions and a marked decrease in IL-17α+ T cells at the dermal–epidermal junction [65]. In another case report, secukinumab was used successfully to treat erosive genital LP refractory to steroids, calcineurin inhibitors, hydroxychloroquine, acitretin, and methotrexate. In this patient, significant improvement was noted at 12 weeks, and complete resolution was noted at 9-month follow-up [66].

Despite reports of successful LP resolution with secukinumab, paradoxical LP eruptions after secukinumab treatment were also reported in the literature. In one report, a patient treated with secukinumab for psoriasis had reemergence of oral LP lesions 1 month after initiating treatment. Secukinumab was discontinued in this patient and lesions resolved after 1 month of treatment with cyclosporine [67]. In another report, a patient experienced oral LP with candidiasis 5 months after treatment with secukinumab for psoriasis. This was the only report of coexisting oral candidiasis with oral LP in our review of the literature, and resolution was achieved after discontinuation of secukinumab and treatment with oral antifungals [68].

Evidence for brodalumab use in LP management was more sparse, with one case report detailing its use. Brodalumab is unique among IL-17 biologic agents as it targets the IL-17 receptor, whereas most agents target the IL-17 cytokine. In this study, a patient with coexisting lichen planopilaris (LPP) and moderate-to-severe plaque psoriasis was treated with brodalumab owing to traditional therapies of methotrexate and cyclosporine being contraindicated. At 3-month follow-up, this patient had > 90% resolution of psoriasis plaques and complete resolution of LPP lesions with no adverse effects. The authors note that the particular efficacy of brodalumab in this patient may be supported by the high levels of IL-17 receptor expressed in follicular epithelial cells [69].

IL-23 Inhibitor Use in Lichen Planus

As with HS and PG, a review of the literature supported tildrakizumab-asmn and guselkumab use in the management of LP. In a prospective cohort of 24 patients with vulvovaginal LP, 21 patients achieved sustained remission of

symptoms on treatment with tildrakizumab-asmn. Mean time to remission was 4.4 months, and 11 of the patients treated were able to achieve remission with tildrakizumab-asmn monotherapy alone. Importantly, side effects were common in this cohort, with the most common being vulvovaginal candidiasis and injection site erythema [70]. Other case reports reinforced tildrakizumab-asmn success for vulvovaginal LP as well as reported success in treatment of gingival LP, erosive oral LP, lichen planopilaris, and lichen planus pemphigoides [71–74]. One case report was reviewed supporting guselkumab use for the management of LP. In this report, a patient with chronic LP lesions of the tongue refractory to traditional immunosuppressives was successfully treated with guselkumab. Complete resolution was achieved at 30 weeks, and remission was durable [65].

Ustekinumab, an IL-23 inhibitor approved for treatment of irritable bowel disease, psoriasis, and psoriatic arthritis, was also reported in the literature for the management of LP; however, evidence was conflicting. In one report, ustekinumab treatment resulted in complete remission of lichen planus pemphigoides in a patient with highly recalcitrant disease. All other immunosuppressives were stopped in this patient and remission was durable [75]. In a separate case report, however, ustekinumab was used to treat psoriasis in a patient with concomitant lichen planopilaris (LPP), however, similar efficacy was not achieved. In this patient, rapid clearing of psoriasis was achieved, but LPP lesions were unchanged at 10-month follow-up. No adverse effects were noted in this report [76].

TNF Inhibitor Use in Lichen Planus

Off-label use of biologics targeting TNF was noted for the treatment of LP, and reports showed efficacy in resolution of lesions. Etanercept is a biologic decoy receptor targeting TNF currently approved for treatment of a variety of seronegative spondyloarthropathies as well as plaque psoriasis. In one report, a patient with annular atrophic LP and concomitant psoriasis was treated with etanercept after failure of traditional disease-modifying antirheumatic drugs (DMARDs), which led to near complete resolution of both disease processes. Importantly, in this patient etanercept was administered alongside potent topical corticosteroids, which had been used alone previously without success [77]. In another report, a patient with oral LP refractory to traditional immunosuppressives was treated with etanercept, with notable clinical improvement noted at 4-week follow-up [78].

Adalimumab, a TNF inhibitor approved for treatment of psoriasis, rheumatoid arthritis, and IBD, among other disorders, was also identified as being used off-label successfully in the treatment of LP. In one report, adalimumab was used to treat cutaneous LP in a patient who had previously failed treatment on corticosteroids, PUVA, and acitretin. In this patient rapid improvement was noted, with itching decreased at 2 weeks and resolution of cutaneous lesions at 2 months. No side effects or recurrence were noted at 6-month follow-up [79]. In another report, adalimumab treatment resulted in resolution of lichen planopilaris in a patient with highly recalcitrant disease. Clinical improvement was noted with a marked reduction in peripilar scaling and erythema [80].

Other Biologic Use in Lichen Planus

Other biologics were reported in the literature for the management of LP with variable efficacy. Rituximab, a biologic targeting CD20 on B cells, was noted in the literature in three separate reports; however, efficacy was not consistent. In one report, rituximab use in a patient with metastatic melanoma and immune checkpoint inhibitor-induced LP demonstrated successful remission of LP symptoms, while the melanoma remained undetectable [81]. Additionally, a case series of rituximab use in two patients with erosive LP demonstrated successful remission within 4 weeks. [82] Efficacy was variable, however, and a case series of five patients receiving rituximab for erosive lichen planus demonstrated failure or transient minimal improvement in LP symptoms. This result

was partially attributed by authors to the older population in the study being associated with a less favorable response to rituximab. Adverse events including grade 3 infusion-related reactions were seen in this cohort [83].

One report was reviewed of successful dupilumab use in the management of cutaneous LP. In this patient, dupilumab was used after failure of corticosteroids, tacrolimus, and acitretin, and remarkable improvement was noted at 4-week follow-up. In this patient, itch intensity score improved from 9/10 to 1/10 [84].

Interestingly, paradoxical LP eruptions after biologic use were reported in literature, notably with omalizumab. Used for treatment of asthma and chronic urticaria, omalizumab is a monoclonal antibody against IgE. In one case report, cutaneous LP eruptions were noted in a patient receiving omalizumab for treatment of chronic urticaria after the eighth dose. Notably, no eruptions had occurred with prior doses, and the patient noted high sun exposure after the eighth dose, which may have contributed to this eruption [85]. In another report of a patient receiving omalizumab for steroid-dependent asthma, two separate cutaneous and oral LP occurrences were noted attributed to biologic use. These eruptions resolved with discontinuation of omalizumab, and a causal relationship was suspected [86].

Summary of Biologic Use in Lichen Planus

IL-17 inhibitors, IL-23 inhibitors, and anti-TNF agents were all identified in the literature as being used off-label in the management of LP, among other biologics such as rituximab and dupilumab. Among IL-17 inhibiting agents, secukinumab and brodalumab showed efficacy in treating various forms of LP; however paradoxical LP eruptions were noted with secukinumab. As with HS and PG, tildrakizumab-asmn and guselkumab showed efficacy among IL-23 inhibitors in treating a broad range of LP morphologies; however, adverse reactions such as vulvovaginal candidiasis and injection site erythema were noted. Evidence for ustekinumab was conflicting, as in one report lichen planus pemphigoides was successfully treated, while in another lichen planopilaris was unresponsive. Unique to LP, TNF blocking agents were being used with success across various LP subtypes in limited patient numbers. Etanercept and adalimumab both showed efficacy in recalcitrant disease, and no adverse events were reported. Among other biologics, rituximab showed efficacy in multiple reports, however, side effects were reported and decreased efficacy was noted in an older study population. Evidence for dupilumab use was lacking, however one case report noted efficacy in treating recalcitrant cutaneous LP. Paradoxical LP reactions were noted in the literature with omalizumab use, and care must be taken to monitor photosensitivity in these patients. The breadth of off-label biologic use in LP management is promising for recalcitrant disease; however, larger-scale trials are necessary to understand the safety and efficacy of these different targeted treatments.

SEBORRHEIC DERMATITIS

Seborrheic Dermatitis (SD) is a chronic, inflammatory dermatosis typically affecting the scalp, face, and trunk. Clinically, SD is characterized by erythematous, scaly patches, and may present with greasy-looking yellowish scale. SD classically worsens during winter months, and relapse is common in a chronic disease course.

Treatment for SD include topical antifungals, steroids, and calcineurin inhibitors as first-line therapy. Additional topicals such as selenium sulfide and janus-kinase inhibitors may also be used depending on areas affected. Oral antifungals may also be used in patients with moderate-to-severe SD who have not had adequate response on topical therapies.

Currently, no biologics are approved for the treatment of SD. Review of the literature did not reveal any off-label biologic use documented in literature for SD, however, paradoxical SD eruptions after dupilumab use were noted in two separate reports.

Paradoxical Seborrheic Dermatitis Reactions with Biologic Use

In one report of two patients treated for atopic dermatitis with dupilumab, SD eruptions were noted 4 months and 7 months after initiation of biologic treatment, respectively. In both patients, there was no history of psoriasis or previous SD, and both patients were treated successfully with traditional SD therapies with resolution of symptoms [87]. In another series of 64 patients treated with dupilumab, one patient was noted to have SD eruptions due to treatment with biologic medication [88].

Summary of Biologic Use in Seborrheic Dermatitis

Evidence for off-label biologic use in the management of SD was lacking in our review of the literature. Interestingly, paradoxical SD eruptions after treatment with dupilumab were noted, and clinicians should be aware of this potential adverse event when using medications that may induce cytokine imbalance due to Th2 inhibition.

CONCLUSION

Review of the literature showed that biologic agents are being used off-label in the management of a variety of immune-mediated skin disease across a range of institutions, and that safety and efficacy are variable dependent on cytokine targets and primary pathologies. In particular, agents targeting IL-17, IL-23, and TNF seemed of particular prevalence in the literature, among other targeted biologics matched to disease morphology. Paradoxical eruptions were reported with biologic use, and clinicians must be conscious of these possible adverse events when such biologic treatments are used. The broad variety, efficacy, and safety of treatments reviewed underscores a need for more thorough investigation of the role these biologics may play in comprehensive management of immune-mediated skin pathologies.

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