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REVIEW ARTICLE



Dupilumab use in dermatologic conditions beyond atopic dermatitis – a systematic review

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ABSTRACT

Importance: While dupilumab has emerged as an effective treatment for moderate-to-severe atopic dermatitis (AD) since its approval in 2017, interleukin-4 and 13 blockade has also demonstrated efficacy in off-label chronic dermatologic conditions.

Objective: To identify chronic dermatologic conditions in which dupilumab has demonstrated efficacy.

Findings: Thirty-three reports of dupilumab use in non-AD dermatologic conditions were identified through systematic literature review. Effective use of dupilumab has been reported in case reports and case series in the treatment of chronic pruritus, prurigo nodularis, eczematous eruption of aging, allergic contact dermatitis, chronic hand eczema, alopecia areata, urticaria, eosinophilic annular erythema, bullous pemphigoid and papuloerythroderma of Ofuji. Clinical trials are underway evaluating the efficacy of dupilumab in allergic contact dermatitis, chronic hand eczema, alopecia areata, chronic spontaneous urticaria and cholinergic urticaria.

Conclusions and relevance: Overlap in immune signaling pathways between AD and chronic pruritus, eczematous eruption of aging, allergic contact dermatitis, chronic hand eczema, alopecia areata, urticaria, eosinophilic annular erythema, bullous pemphigoid and papuloerythroderma of Ofuji make these conditions candidates for dupilumab therapy when standard treatments have failed or are contraindicated. While promising as a therapeutic option, off-label prescribing of dupilumab requires consideration of challenges in insurance authorization and out-of-pocket cost to the patient.

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Dupilumab; off-label; pruritus; urticaria; contact dermatitis; alopecia areata; hand eczema

Introduction

Dupilumab is a monoclonal antibody against the interleukin (IL)-4 receptor alpha subunit, common to both the IL-4 and IL-13 receptors, and is currently approved for the treatment of moderate-to-severe atopic dermatitis (AD) and asthma in patients over 12 years of age (1). Blockade of IL-4 and IL-13 signaling inhibits T_H2-driven inflammation central to a number of atopic and inflammatory skin conditions. While dupilumab has demonstrated impressive efficacy in AD, it also demonstrates therapeutic promise in a number of reports for chronic treatment-refractory dermatoses including chronic pruritus, eczematous eruption of aging, allergic contact dermatitis (ACD), hand eczema (HE), alopecia areata (AA), urticaria, autoimmune bullous diseases and papuloerythroderma of Ofuji. The efficacy of dupilumab in ACD (2), HE (3), AA (4), chronic spontaneous urticaria (5) and cholinergic urticaria (6) is currently being investigated in clinical trials. This systematic review aims to synthesize reports on the successful off-label use of dupilumab in chronic dermatologic conditions, addresses prudent considerations for off-label dupilumab prescribing, and highlights future investigative directions for expanded applications of dupilumab in dermatology.

Methods

In June 2019, two research personnel conducted a systematic literature review via PubMed, Google Scholar, and clinicaltrials.gov databases using the search term “dupilumab”. Review articles, reports regarding non-dermatologic disease and non-English publications were excluded. The resulting records were further refined through abstract and full-text review, excluding trials that failed to demonstrate efficacy and publications pertaining to AD. Clinical trials, case series and case reports in non-AD dermatologic conditions were included. Implementing these search criteria, a total of 33 records were selected for evaluation in this review. Stepwise search results are documented in the PRISMA flow diagram (Figure 1). Quality of individual studies was assessed according to the rating scheme modified from the Oxford Center for Evidence-based Medicine (7).

Results

Chronic pruritus and prurigo nodularis

Chronic pruritus involves a complex interplay between inflammatory signaling and neurocutaneous sensation (8).

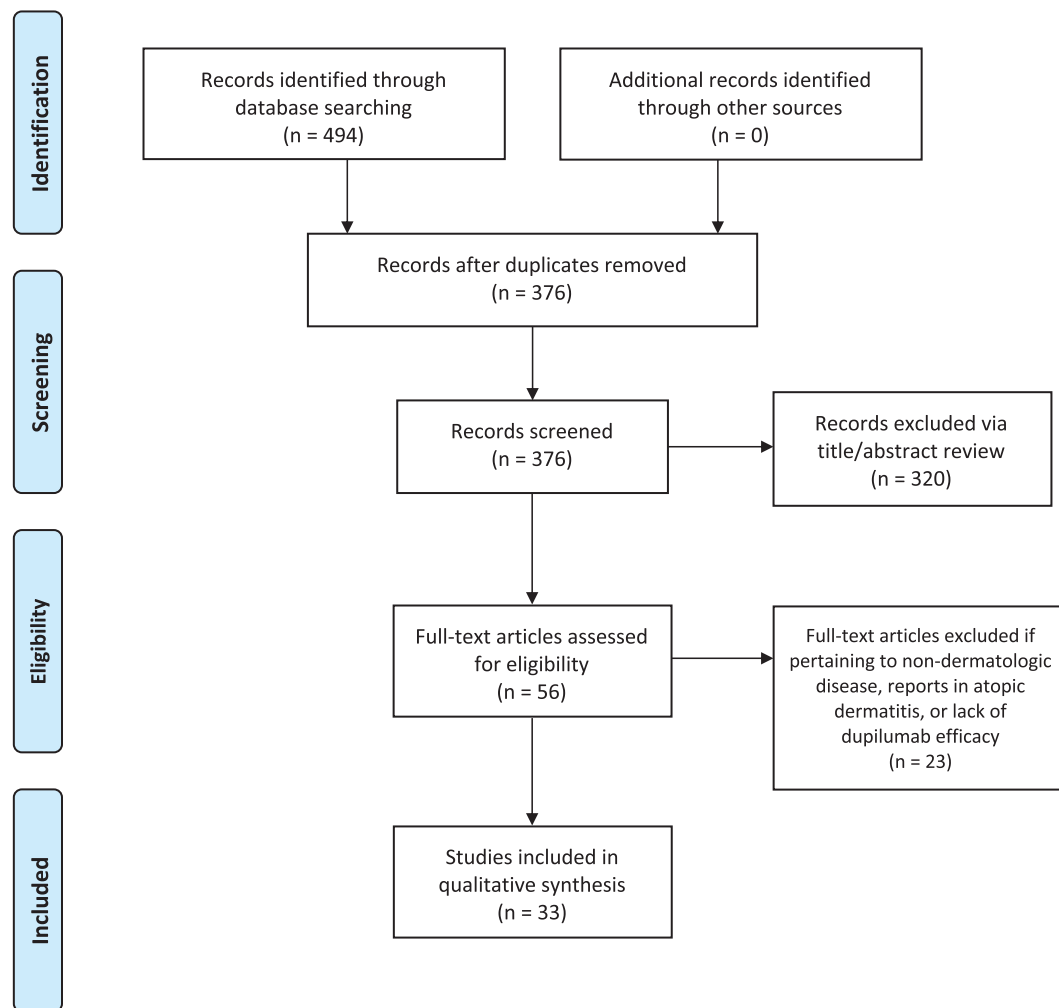


Figure 1. PRISMA flow diagram. Stepwise literature search results in systematic review of dupilumab use in dermatologic conditions beyond atopic dermatitis.

Prurigo nodularis (PN) is a severe form of generalized chronic pruritus manifesting as firm, excoriated, hyperkeratotic nodules. Chronic itch involves nonhistaminergic neuronal pathways, and IL-4 and IL-13 have been identified as pruritogens in chronic itch via IL-4 receptor- α -mediated activation of cutaneous small unmyelinated C fibers (9,10). T_H2 cytokines induce STAT6 activation in PN (11), suggesting a potential therapeutic role for dupilumab through IL-4 and 13 inhibition. Furthermore, up to 50% of PN patients have a history of atopy (12). Currently, there is no FDA-approved treatment for PN, which is often refractory to topical, intralesional and systemic corticosteroids, phototherapy and neuropathic pain agents such as gabapentin. Additional interventions include behavioral therapy to decrease excoriation and mood modulators such as selective serotonin and norepinephrine reuptake inhibitors.

Several cases support the off-label use of dupilumab in patients with poorly-controlled PN and demonstrate improvement in both clinical signs of prurigo nodules and patient-reported itch (13–16). Eight patients with long standing PN of 5–15 years reported an average 7.3–8.8 point reduction on the pruritus numerical rating scale (NRS) after 12 weeks of dupilumab therapy, with reduction in prurigo nodule size, number and erythema (13–15).

Dupilumab has also been used to successfully treat a case of long-standing uremic pruritus secondary to polycystic kidney disease (17). Previously failed therapies included narrow band UVB, doxepin, aprepitant, gabapentin, pregabalin, naltrexone, mirtazapine, topical corticosteroids and pramoxine. While continuing on narrow band UVB and gabapentin, dupilumab was initiated at AD dosing with near complete resolution of pruritus (8/10 to 1/10 peak pruritus NRS) by 6 months and significant improvement in sleep disturbance and quality of life (12/30 to 1/30 Dermatology Life Quality Index), allowing for discontinuation of concomitant gabapentin therapy.

Eczematous eruption of aging

Idiopathic chronic eczematous eruption of aging (CEEAA) manifests in elderly patients as intensely pruritic eruptions involving the trunk and extremities, often more prominent over photo-distributed sites. The aging immune system undergoes a process of senescence that leads to a T_H2 -predominant response which causes itch (18). CEEAA is a diagnosis of exclusion that should be made after workup for AD, contact dermatitis, drug reaction, cutaneous T-cell lymphoma and scabies infestation. While commonly idiopathic, CEEAA can be

associated with medication exposure, most commonly thiazides and calcium channel blockers (19). Topical corticosteroids are frequently ineffective for control of itch, and broadly immunosuppressive agents such as corticosteroids, methotrexate and cyclosporine are not preferred in the elderly due to concern for osteopenia and hepatic and renal toxicity.

In a case of a 66-year-old man with a 3-year history of intensely pruritic idiopathic CEAA involving the trunk and bilateral upper and lower extremities that had been unresponsive to topical, oral and intramuscular corticosteroids, methotrexate and mycophenolate mofetil (MMF), dupilumab at AD dosing led to rapid and complete resolution of itch and dermatitis maintained through 4-month follow-up (20). Notably, this patient elected to cash pay for dupilumab to avoid delay in treatment pending insurance authorization for off-label use.

Chronic anogenital pruritus

Common etiologies of chronic anogenital pruritus include ACD (frequently due to soaps or hygiene products) and fungal or bacterial infection, exacerbated by friction and occlusion. Additional etiologies include lumbosacral spinal injury, stenosis or arthritis. Patch testing can aid in identification of potential irritants and allergenic culprits. Management is challenging because trigger avoidance is often difficult and topical anti-inflammatory anesthetic agents have limited efficacy in ameliorating itch (21). In a 62-year-old man with L5–S1 anterolisthesis and chronic pruritic papular anogenital eruption refractory to topical corticosteroids, antifungals, oral antihistamines and MMF, dupilumab led to near complete resolution of anogenital itch and dermatitis after only 1 month with response maintained at 1-year follow-up (22).

Allergic contact dermatitis

Immune signatures of allergic contact dermatitis (ACD) vary according to allergen type, but typically involve T_H1 , T_H2 , T_H17 , and T_H22 signaling pathways (23). T_H2 polarization in some forms of ACD suggests a therapeutic role for dupilumab. As standard of care for ACD involves trigger avoidance and use of topical and systemic corticosteroids, the utility of dupilumab for ACD is in cases where trigger avoidance is impractical (with multiple allergens), impossible (as in occupational exposure), or where a trigger cannot be identified despite expanded patch testing.

Dupilumab has demonstrated efficacy in treatment of ACD in several separate case reports and a retrospective chart review (24–29). Among these, a total of 26 patients with patch test-proven ACD to various allergens (including textile, rubber, nickel, cocamidopropyl betaine, nickel, oleamidopropyl dimethylamine and fragrance mix) were refractive to topical corticosteroids and a number of systemic agents including prednisone, methotrexate, MMF and cyclosporine. When treated with dupilumab, all patients experienced rapid and drastic improvement of symptoms with up to 90% body surface area (BSA) improvement in as early as 3 weeks (range 3–12 weeks at follow-up) (24–28). Among

these is a case involving a 44-year-old man with long-standing generalized ACD to nickel triggered by his endovascular stents and vascular clip, an example of ACD in which trigger avoidance is impossible. He experienced significant improvement within 8 weeks after starting dupilumab, and was tapered off prednisone and MMF after 6-year courses (25).

A retrospective chart review of 64 AD patients found no differences in response to dupilumab among AD-only vs. AD + ACD patients (as measured by BSA, Investigator Global Assessment (IGA) score and pruritus rating) (29). The authors postulated that in AD patients with concomitant ACD, dupilumab may improve symptoms by dampening of IL-4/13 signaling common to both conditions. Alternatively, treatment of AD may bolster skin barrier integrity and decrease permeability to allergens.

An upcoming open-label phase 4 trial will investigate the use of dupilumab in up to 20 ACD patients who have not improved with 6 months of allergen avoidance (2). Subjects will receive dupilumab at AD dosing with a 600 mg loading dose followed by 300 mg maintenance doses every two weeks over a 12-week treatment period. The primary endpoint is change in IGA at week 12, with secondary endpoints evaluating change in BSA, Eczema Area and Severity Index, itch NRS, Dermatology Life Quality Index and sleep quality.

Chronic hand eczema

Chronic hand eczema (CHE) is a common and debilitating condition with significant diagnostic and management challenges. Clinical manifestations are highly variable, but involve intensely pruritic and painful areas of erythema, edema and fissuring, causing a significant negative impact on patients' activity level and quality of life (30). It is a heterogeneous diagnosis encompassing several etiologies, including allergic and irritant contact dermatitis (often occupational or household exposures) and atopic hand dermatitis, with morphologic classifications including dyshidrotic (vesicular) and hyperkeratotic hand dermatitis (31). Treatment approaches for CHE include allergen or irritant avoidance along with topical corticosteroids, calcineurin inhibitors and janus kinase inhibitors, as well as systemic therapies including retinoids and traditional immunosuppressive agents (32). Treatment for the hyperkeratotic subtype involves topical keratolytics such as urea, ammonium lactate and salicylic acid, and systemic retinoids including acitretin and alitretinoin (32).

Significant overlap exists between inflammatory pathways involved in CHE and AD, with elevation of T_H2 cytokines IL-4 and 13 in atopic hand eczema (HE) and IL-4-driven keratinocyte proliferation in hyperkeratotic HE (32). Dyshidrotic HE may be associated with atopy or with occupational allergens or irritants (33). Some specific allergens in ACD induce a T_H2 -predominant inflammatory response (23), indicating a potential therapeutic application of dupilumab in blockade of IL-4 and 13 in atopic, hyperkeratotic, dyshidrotic and ACD-associated forms of CHE.

Dupilumab has been used with success in a total of seven cases of recalcitrant CHE including ACD, atopic and dyshidrotic types (34–37). Previously failed management included trigger avoidance and topical and systemic immunosuppressives and immunomodulators. Notably, two dyshidrotic HE patients had also failed phototherapy, excimer laser therapy, apremilast, efalizumab, etanercept, adalimumab, ixekizumab, systemic and subcutaneous methotrexate, MMF and cyclosporine. Dupilumab treatment led to significant improvement or complete clearance of eczematous manifestations, symptoms and/or quality of life in as early as 4 weeks and maintained at 2–4-month follow-up.

A recent single-center retrospective review assessed clinical response in 11 patients treated with dupilumab for at least 3 months, with subsets of patients with dermatitis involving the body-only, body and hands, and hands-alone (38). Within this cohort, prior ineffective therapies included prednisone, cyclosporine and MMF. The vast majority of patients with hand dermatitis reported improvement in pruritus (97%), pain (100%) and fissuring (100%) at previously lesional sites, with complete resolution of fissures reported by 10 of 11 patients with fissuring at baseline.

A prospective observational study of 47 patients with CHE and concomitant AD evaluated the effect of dupilumab on Hand Eczema Severity Index (HECSI) score after 16 weeks on dupilumab (39). Subjects had previously failed therapies including methotrexate, azathioprine, cyclosporine and oral prednisolone, and concomitant use of topical corticosteroids or calcineurin inhibitors was permitted during the study period. Sixty percent (28/47) of patients achieved a 75% reduction in HECSI score, and with a mean 49.2-point reduction in HECSI at 16 weeks.

An upcoming phase 2 trial based in France will evaluate the efficacy of dupilumab versus placebo in moderate-to-severe CHE refractory to high potency topical corticosteroids (3). Up to 94 subjects will be enrolled in this randomized, double-blind placebo-controlled study, and will receive either dupilumab at a 600 mg loading dose with 300 mg biweekly maintenance doses or placebo at the same injection schedule for 16 weeks. The primary endpoint is change in modified Total Lesion Symptom Score, which evaluates signs and symptoms of CHE including erythema, scaling, lichenification/hyperkeratosis, vesiculation, edema, fissures and pruritus/pain. Secondary endpoints include change in pruritus, pain, quality of life, and sleep loss from baseline to week 16.

Alopecia areata

Alopecia areata (AA) is an inflammatory non-scarring hair loss characterized by perifollicular lymphocytic inflammation. AD patients hold a 26-fold greater risk of developing AA compared to healthy controls (40), likely because the two conditions share common inflammatory signaling pathways including T_H2 overactivation with upregulation of IL-4 and IL-13 (41). Due to this overlap, dupilumab has been trialed in patients with concomitant AA and AD. To date, five cases have been published documenting hair regrowth in AD patients with long-standing AA or alopecia universalis

after dupilumab initiation (42–46). In these reports, history of AA ranged from 1 to 8 years and progressed to alopecia universalis or totalis in four of five cases. Previously failed therapies included topical corticosteroids, methotrexate, cyclosporine and prednisone. Hair regrowth was observed within 6 weeks to 3 months after dupilumab initiation, with complete or near complete scalp hair and partial eyebrow regrowth by 6–12 months.

The efficacy of dupilumab in treatment of AA is currently being evaluated in a phase 2 trial (4). In this randomized, double-blind, placebo-controlled study of 54 moderate-to-severe AA patients with and without concomitant AD, subjects will receive either dupilumab at a loading dose of 600 mg followed by 300 mg every two weeks or placebo according to the same injection schedule over 48 weeks. Primary endpoints are change in Severity of Alopecia Tool (SALT) score from baseline to 24 and 48 weeks.

Interestingly, while a number of case reports describe hair regrowth in patients with concomitant AD and AA treated with dupilumab, there are also several cases of new-onset AA after dupilumab initiation (47). Further investigation of the relationship between dupilumab and AA may help to elucidate the mechanisms underlying these conflicting observations.

Urticaria

Chronic urticaria can be classified as either inducible or spontaneous and occurring with or without angioedema for >6 weeks (48). Due to its idiopathic nature, chronic spontaneous urticaria (CSU) can be challenging to treat and frustrating to both patients and providers. The pathogenesis of CSU involves basophil and mast cell degranulation and histamine release, and a mixed T_H1/T_H2 response of IL-4, IL-5 and interferon- γ cytokines, with potential for inhibition of IL-4-driven IgE production via dupilumab. Treatment options include high-dose second generation non-sedating antihistamines and omalizumab, an anti-IgE monoclonal antibody. Cyclosporine is a third-line treatment option due greater risk of associated adverse effects (48).

Dupilumab has been used successfully to treat a case of CSU with episodic angioedema involving a 40-year-old atopic woman with AD and environmental and food allergies (49). The patient's CSU did not improve on 600 mg (doubled dose) of omalizumab monthly or on prednisone. Following discontinuation of omalizumab, dupilumab was initiated at standard AD dosing, with resolution of CSU within 3 months. The authors cited five other instances of CSU resolving with dupilumab in patients previously refractory to omalizumab (49).

In accordance with these reports, dupilumab's efficacy and safety in CSU is being investigated in a phase 2 trial in Germany (5). In this multicenter double-blind, placebo-controlled study, 72 adults with CSU (with or without angioedema) refractory to antihistamines for >6 weeks will be randomized to receive either dupilumab or placebo for 16 weeks. The primary endpoint is change in urticaria activity score over 7 days (UAS7) from 7 days prior to baseline to 7 days prior to week 16.

The efficacy of dupilumab is also being assessed in cholinergic urticaria refractory to antihistamines, which manifests as small hives induced by elevation of core temperature, with triggers including exercise, warm baths and emotional stress (50). This phase 2 multicenter trial in Germany is a randomized, double-blind placebo-controlled trial comparing the effect of dupilumab at 600 mg subcutaneous loading dose and 300 mg maintenance dose every 2 weeks to placebo at the same dosing schedule over 16 weeks (6). The primary endpoint is change in cholinergic urticaria activity score over 7 days (CholUAS7) from 7 days prior to baseline to 7 days prior to week 16.

Eosinophilic annular erythema

Eosinophilic annular erythema (EAE) is a rare dermatosis with fewer than reported 30 cases that presents with recurrent asymptomatic or pruritic annular erythematous plaques with central hyperpigmentation on the trunk and extremities. There is some controversy as to whether EAE is a distinct entity or exists on a spectrum of Wells syndrome, also known as eosinophilic cellulitis (51). In EAE, eosinophilia is variably present on laboratory workup and characteristic histologic findings include basal melanosis and interstitial lymphocytic and eosinophilic dermal inflammation without flame figures (as seen in Wells syndrome) (52). EAE may persist or resolve spontaneously, but is often refractory to treatment with topical and systemic steroids and hydroxychloroquine (51). Dupilumab's proposed efficacy in EAE derives from inhibition of eosinophilic T_H2 inflammation via IL-4 and IL-13 blockade (53).

One case report describes resolution of biopsy-proven EAE with dupilumab (54). A 14-year-old girl presented with a 4-month history of pruritic annular plaques symmetrically over the trunk, extremities and forehead. Punch biopsy demonstrated acute spongiotic dermatitis with pronounced intravascular and dermal eosinophils, and laboratory findings included marked eosinophilia at 11.3% (normal range 1.0–3.0%). After failure of topical and oral steroids, dapsone and tofacitinib over a period of 10 months, she was started on dupilumab at AD dosing. Lesions and pruritus completely resolved within two weeks, and she remained clear at 5 months on continued biweekly maintenance dosing.

Bullous pemphigoid

Bullous pemphigoid (BP) is an autoimmune blistering disease caused by IgG and C3 deposition with antibodies directed against BP180 and BP230, components of hemidesmosomes in basal keratinocytes. BP manifests as widespread pruritic, tense subepidermal blisters especially pronounced at frictional sites. Neutrophilic, lymphocytic and eosinophilic inflammation is evident histologically. BP has been found to involve a mixed T_H1/T_H2 inflammatory response, with elevation of a number of cytokines (including IL-4) identified in skin, serum and blister fluid (55).

Dupilumab has been used in one case of BP recalcitrant to prednisone (56). An 80-year-old man with a 6-week

history of tense bullae over the trunk and extremities was diagnosed with BP, confirmed by direct immunofluorescence. He was treated with prednisone but began to flare as prednisone dose was tapered. Use of immunosuppressive agents was limited by a history of tuberculosis and hepatitis B exposure. Therefore, he was started on dupilumab at standard dosing, and pruritus improved within one week. All blisters had resolved by 3 months of dupilumab treatment, and previously elevated serum levels of BP180 and BP230 antibodies became undetectable. The patient remained clear at 10 months while continuing on dupilumab.

Papuloerythroderma of Ofuji

First described in 1984, papuloerythroderma of Ofuji (PEO) is characterized by pruritic, widespread coalescing papules that spare the skin folds (“deck-chair sign”) (57,58). PEO most commonly occurs in older males and has been found to be associated with medication exposure, infection or internal malignancy (57,59). Laboratory findings in PEO include peripheral eosinophilia and elevated IgE, indicative of a T_H2 -driven process (58,59). Recent studies have identified markedly increased IL-4 and IL-13 production by T cells in patients with PEO (60), supporting a potential therapeutic role for dupilumab.

A recent case series described resolution of PEO in two patients treated with dupilumab (61). Duration of PEO was one and seven years, and comprehensive screening for internal malignancy was negative in both cases. Following failure of multiple courses of topical and systemic corticosteroids, the patients were initiated on dupilumab with significant improvement in lesions by 2–4 months and reduction of pruritus visual analog scale from 10 at baseline to 0 at 6 months. Dupilumab injection frequency was decreased to every 4–6 weeks, with remission of PEO maintained at 9–10-month follow-up (61).

Reports of successful off-label use of dupilumab in dermatologic conditions are summarized in Table 1.

Summary

With the approval of dupilumab in 2017, we have entered an exciting era of targeted dermatologic therapy via IL-4/13 blockade. In addition to its impressive efficacy in treatment of AD, dupilumab also shows promise in treatment of a number of other conditions including chronic pruritus, eczematous eruption of aging, ACD, hand eczema, alopecia, urticaria, eosinophilic annular erythema, bullous pemphigoid and papuloerythroderma of Ofuji. Looking toward broadened applications of dupilumab in dermatology, more thorough mechanistic understanding of its efficacy in these conditions is warranted. The current literature on off-label use of dupilumab is limited by small sample size and a lack of randomized controlled trials. In most reports, dupilumab was initiated as a trial following failure of multiple treatments, and the mechanisms underlying dupilumab's efficacy in these off-label conditions remain largely unknown.

Table 1. Effective off-label use of dupilumab in dermatologic conditions.

Condition	Study type (n)	Level of evidence	Past medical history/comorbidities	Prior failed therapies	Concomitant medications during dupilumab treatment	Time to response and clinical improvement	Proposed mechanism of dupilumab efficacy
Prurigo nodularis (13)	Case series (3)	4		IM, PO, IL, topical steroids, hydroxyzine, doxepin, gabapentin, cryotherapy, phototherapy	Goeckerman therapy, antihistamines, gabapentin, pregabalin, thalidomide, CyA, dronabinol	4 weeks* Flattening of nodules and decrease in erythema, -7.7 mean reduction in pruritus NRS 2-4 weeks* -8.8 mean reduction in pruritus NRS 3 months* Flattened prurigo nodules, decreased size and number 8 months: residual lichenified papules and post-inflammatory hyperpigmentation, -8.5 reduction in pruritus NRS from baseline 4 weeks* Patient 1: significant improvement in pruritus after 2 doses; d/c due to alopecia Patient 2: rapid reduction of pruritus with dramatic skin clearance maintained at 1 year	Blockade of IL-4/13-mediated activation of nonhistaminergic neuronal pathways underlying chronic itch. Inhibition of IL-4/13-driven STAT6 activation in PN
Prurigo nodularis (14)	Case series (4)	4	Childhood AD (1/4)	TCS, mirazapine, topical calcineurin inhibitors, narrowband UVB			
Prurigo nodularis (15)	Case report (1)	5	Childhood AD and allergic conjunctivitis	TCS, cryotherapy, hydroxyzine, phototherapy, dapsone, MTX, thalidomide, CyA			
Prurigo nodularis (16)	Case series (2)	4	Hyperlipidemia, hypothyroidism	Topical, PO, IL steroids, antihistamines, doxepin, narrow/broad-band UVB, naltrexone, gabapentin, etanercept, ustekinumab, apremilast, tofacitinib, MTX, MMF, CyA, lenalidomide, thalidomide			
Uremic pruritus (17)	Case report (1)	5	Polycystic kidney disease, renal transplant	NBUVB, doxepin, aprepitant, gabapentin, pregabalin, naltrexone, mirazapine, topical corticosteroids, pramoxine	NVUVB, gabapentin	6 months* Decrease in peak pruritus NRS (8/10-1/10), improvement in sleep disturbance and quality of life (12/30-1/30 DLQI), gabapentin d/c 2 months* Complete resolution of itch and eczematous eruption	Blockade of IL-4/13-mediated activation of nonhistaminergic neuronal pathways underlying chronic itch. Potential effect of dupilumab in decreasing production of IL-31 by T _H 2 cells Dampening of IL-4/13-driven eosinophilic inflammation (variably present in CEEA). Reduction of cutaneous sensory nerve activation in chronic pruritic component
Chronic eczematous eruption of aging (20)	Case report (1)	5	Hypertension, hyperlipidemia, corticosteroid-induced osteopenia	IM, PO, topical steroids, MTX, MMF			
Chronic anogenital pruritus (22)	Case report (1)	5	Asthma, allergic rhinitis, ADHD, depression, L5-S1 anterolisthesis	Contact and food allergen avoidance, TCS, topical antifungals, antihistamines, MMF	Topical lidocaine cream	1 month* Resolution of perianal and genital dermatitis, 95% improvement in pruritus; maintained at 12 months 4-6 months*	Blockade of IL-4/13-mediated activation of nonhistaminergic neuronal pathways underlying chronic itch
Allergic contact dermatitis (24)	Case series (2)	4	Patient 1: Enlarged thyroid, lung nodule, TB Patient 2: hypertension, nasal allergies, fibromyalgia, type 2 diabetes, thyroid dysfunction, dyspepsia Childhood AD (1/3), seasonal allergies	Topical and PO steroids, MTX, MMF	TCS, tacrolimus	Decreased BSA involvement, significant reduction in pruritus, improved sleep quality 3-6 weeks* >90% improvement in BSA involvement; maintained at 6-13 months 8 weeks* Significant improvement in dermatitis and pruritus	Blockade of T _H 2 IL-4/13 signaling underlying some allergen-specific forms of ACD
Allergic contact dermatitis (27)	Case series (3)	4		Prednisone, azathioprine, CyA			
Allergic contact dermatitis (25)	Case report (1)	5	Hypercoagulability	TCS, prednisone, MMF	Prednisone, MMF after dupilumab initiation)		

(continued)

Table 1. Continued.

Condition	Study type (n)	Level of evidence	Past medical history/comorbidities	Prior failed therapies	Concomitant medications during dupilumab treatment	Time to response and clinical improvement	Proposed mechanism of dupilumab efficacy
Allergic contact dermatitis (28)	Retrospective chart review (15)	3	Childhood AD, hand dermatitis	Prednisone, azathioprine, MMF, CyA, MTX		10–12 weeks* Mean 85% improvement in BSA involvement	
Systemic allergic contact dermatitis (26)	Case series (5)	4	Childhood AD (4/5)	MMF, MTX, CyA, prednisone, phototherapy		4–6 weeks* 80–100% improvement in BSA involvement, reduction in pruritus	Blockade of T_H2 IL-4/13 signaling underlying systemic allergy to Balsam of Peru and nickel
Allergic contact dermatitis (29)	Retrospective chart review (64)	3		Phototherapy, unspecified immunosuppressants, corticosteroids		No significant difference in IGA improvement between AD patients with and without ACD –2.1 IGA reduction in patients with confirmed ACD; –2.2 in patients with suspected ACD; –2.5 in those without ACD –6 weeks to 3 months*	Dampening of IL-4/13 signaling common to AD and ACD. Improvement in AD via dupilumab may bolster skin barrier integrity and decrease permeability to allergens
Chronic hand eczema (34)	Retrospective chart review (3)	3	Seasonal allergies (1/3)	Topical and PO steroids, MTX, CyA, MMF		80–100% improvement in CHE 4 weeks*	Inhibition of IL-4/13 in atopic HE, IL-4-driven keratinocyte proliferation in hyperkeratotic HE
Chronic hand eczema (35)	Case report (1)	5	AD, asthma, rhinitis, family history of atopy	Allergen avoidance, TCS, phototherapy	Prednisolone (tapered and discontinued after 12 weeks on dupilumab)	Reduction in HECSI from 244/360 (very severe) at baseline to 115 (severe) at 4 weeks to 11 (almost clear) by 16 weeks	and T_H2 signaling in some forms of ACD-associated CHE
Chronic hand eczema (38)	Retrospective review (11)	3	AD	Prednisolone, CyA, MMF		Improvement in pruritus in 97% of patients, pain in 100%, and fissuring in 100%. 10/11 with fissuring reported complete resolution	
Chronic hand eczema (39)	Prospective observational study (47)			CyA, MTX, azathioprine, topical and PO steroids	TCS, TCI	Significant improvement observed by week 4* 75% reduction in HECSI score achieved by 60% of subjects at week 16*	
Dyshidrotic hand eczema (36)	Case series (2)	4	Asthma, seasonal allergies, osteoarthritis, hypertension	Topical and PO steroids, emollients, phototherapy, excimer laser, apremilast, efalizumab, etanercept, adalimumab, ixekizumab, MTX, MMF, CyA	CyA (in 1 patient; tapered and discontinued after starting on dupilumab)	8 weeks to 4 months* Resolution of erythema and fissuring, significant improvement in quality of life	Inhibition of IL-4/13 dampens atopic signaling pathways likely underlying dyshidrotic HE
Dyshidrotic palmoplantareczema (37)	Case report (1)	5	Asthma, hyperlipidemia, impaired glucose tolerance	TCS, tacrolimus, urea cream, cetirizine, hydroxyzine, excimer laser		4 weeks* Improved ambulation (plantar involvement), reduction in pruritus. Complete clearance at 8 weeks	
Alopecia areata (42)	Case report (1)	5	AD, asthma	CyA, MTX		3 months* Scalp hair regrowth with near full regrowth by 6 months	Dampens T_H2 overactivation and upregulation of IL-4/13 (among other elevated cytokines interferon- γ ; IL-23, IL-9) in AA
Alopecia areata (43)	Case report (1)	5	AD	MTX, prednisone		6 weeks* Vellus hairs observed on scalp with near complete terminal hair regrowth over the scalp by 11 months	
Alopecia areata (44)	Case report (1)	5	AD	Topical and PO steroids, omalizumab, CyA		6 months* Patchy scalp hair regrowth with full regrowth by 12 months; regrowth of eyebrow, axillary and pubic hair	

(continued)

Table 1. Continued.

Condition	Study type (n)	Level of evidence	Past medical history/comorbidities	Prior failed therapies	Concomitant medications during dupilumab treatment	Time to response and clinical improvement	Proposed mechanism of dupilumab efficacy
Alopecia areata (45)	Case report (1)	5	AD	Topical and PO steroids, calcineurin inhibitors, phototherapy, MTX		8 months* Full scalp hair and some eyebrow regrowth 3 months*	
Alopecia areata (46)	Case report (1)	5	AD	Topical and PO steroids		Improvement in SALT score from 61.6 at baseline to 8 at 3 months* Resolution of CSU	
Chronic spontaneous urticaria (49)	Case report (1)	5	AD, food & environmental allergies, joint pain, autoimmune hypothyroidism	Prednisone, omalizumab		3 months*	Impedes T_H2 /IgE-driven mast cell degranulation and histamine release, targets IL-4 component of mixed T_H1 / T_H2 inflammation in CSU (IL-4, IL-5, interferon- γ)
Eosinophilic annular erythema (54)	Case report (1)	5	Eczematous dermatitis	Topical and PO steroids, dapson, tofacitinib		2 weeks* Complete resolution of annular plaques and pruritus, maintained at 5 months	Inhibition of cutaneous eosinophilic inflammation via IL-4/13 blockade
Bullous pemphigoid (56)	Case report (1)	5	TB exposure, prior hepatitis B infection	Prednisone		1 week* Improvement in pruritus at 1 week with complete resolution of blisters and undetectable BP180 and BP230 antibodies by 3 months, maintained at 10 months	Mixed T_H1 / T_H2 inflammatory response in BP, with elevation of a number of cytokines (including IL-4) identified in skin, serum and blister fluid
Papuloerythroderma of Ofuji (61)	Case series (2)	4	Screening for malignancy negative	Topical and PO steroids		2–4 months* Reduction in pruritus VAS from 10 at baseline to 0 at 6 months; resolution of lesions and pruritus maintained at 9–10 months	T_H2 -driven inflammation in PEO with peripheral eosinophilia, elevated serum IgE, increased IL-4/13 production by T cells

*Dupilumab administered at standard AD dosing in all cases/trials; 600 mg subcutaneous loading dose, 300 mg subcutaneous maintenance dose every other week.

AA: alopecia areata; BP: bullous pemphigoid; BSA: body surface area; CEEA: chronic eczematous eruption of aging; CHE: chronic hand eczema; CSU: chronic spontaneous urticaria; CyA: cyclosporine A; d/c: discontinued;

DLQI: Dermatology Life Quality Index; HE: hand eczema; HECSI: Hand Eczema Severity Index; IL: intralesional; IL- IM: intramuscular; MMF: mycophenolate mofetil; MTX: methotrexate; PEO: papuloerythroderma of Ofuji;

PO: oral; NRS: numerical rating scale; PN: prurigo nodularis; SALT: Severity of Alopecia Tool; TCI: topical calcineurin inhibitors; TCS: topical corticosteroids; UVB: ultraviolet B; VAS: visual analog scale.

Quality Rating Scheme for Studies and Other Evidence – modified from the Oxford Center for Evidence-based Medicine (7)

- 1 Properly powered and conducted randomized clinical trial; systematic review with meta-analysis
- 2 Well-designed controlled trial without randomization; prospective comparative cohort trial
- 3 Case-control studies; retrospective cohort study
- 4 Case series with or without intervention; cross-sectional study
- 5 Opinion of respected authorities; case reports

Furthermore, all treatment regimens followed FDA-approved dupilumab dosing for AD, and the optimal dosing may differ in various dermatologic conditions. While phase 2 trials are underway evaluating the role of dupilumab in hand eczema, AA and urticaria, additional phase 2 and 3 trials are needed to further characterize dupilumab's therapeutic potential in other diseases where dupilumab has been found successful in case reports and small retrospective trials.

As dupilumab is used off-label in all instances in this discussion, insurance authorization and cost to the patient are critical considerations when weighing the benefits of prescribing dupilumab for off-label indications. In cases where traditional immunosuppressive agents are contraindicated due to infectious history, insurance approval for off-label dupilumab may be more readily justified. Despite the practical challenges of obtaining dupilumab for off-label use, its efficacy in many treatment-refractory dermatologic conditions illuminates a promising path ahead for patients, providers and pharmaceutical development.

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AJH has no conflicts of interest to declare.

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