



Review Article

Dupilumab: Evaluating its role in atopic dermatitis, prurigo nodularis, eczemas, urticaria, alopecia areata and vesiculobullous disorders

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ABSTRACT

Dupilumab is a fully human monoclonal IgG4 antibody that targets IL-4 and IL-13 signaling pathways. It is approved by the US-FDA for the treatment of atopic dermatitis and prurigo nodularis. Besides, it has shown efficacy in various off-label dermatologic conditions. This review will elaborate on the utility of dupilumab in atopic dermatitis, prurigo nodularis, eczemas, urticaria, alopecia areata and vesiculobullous disorders.

Keywords: Dupilumab, Atopic dermatitis, Prurigo nodularis, Vesiculobullous disorders, Alopecia areata

INTRODUCTION

Dupilumab is a fully human monoclonal immunoglobulin 4 (IgG4) antibody, which has been approved by the United States Food and Drug Administration for the treatment of moderate-to-severe atopic dermatitis (AD) in adults/pediatric patients (>6 months of age), and prurigo nodularis (PN).^[1,2] Besides, it has also shown efficacy in various off-label dermatologic conditions. The aim of this narrative review is to describe the utility of dupilumab in approved dermatoses as well as its implication in off-label dermatologic disorders.

PHARMACOKINETICS

Following a 600 mg subcutaneous (SC) injection of dupilumab, maximum serum concentrations are attained within 7 days, with steady state concentrations available by week 16. Bioavailability of dupilumab is 64% and its $t_{1/2}$ ranges from 11.7 to 20.5 days.^[3,4] Being a human monoclonal IgG4 antibody, degradation of dupilumab occurs through catabolic pathways into small peptides similar to endogenous IgG. It is considered that following degradation, elimination occurs through the renal route.^[3]

ADMINISTRATION AND DOSING

Dupilumab is administered subcutaneously. The recommended dose is 300 mg every fortnight, after an initial loading dose of 600 mg (given as two 300 mg injections at different sites).^[3] However, some studies suggest weekly administration of 300 mg of dupilumab to be equally or even more effective than the current approved dosing schedule.^[5,6]

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METHODS

PubMed, MEDLINE, and Embase databases were searched from the period January 1, 2014, to March 15, 2024. Searched terms were “dupilumab” or “Dupixent” in combination with the following: “atopic dermatitis,” “prurigo nodularis,” “chronic hand eczema (CHE),” “allergic contact dermatitis (ACD),” “alopecia areata (AA),” “chronic urticaria,” “bullous pemphigoid (BP),” “pemphigoid gestationis (PG),” “Brunsting Perry pemphigoid (BPP),” “epidermolysis bullosa pruriginosa (EBP),” “Grover’s disease (GD),” “Hailey-Hailey disease (HHD),” “pemphigus vulgaris (PV),” “lichen planus (LP),” “lichen planus pemphigoides (LPP),” “Kimura’s disease (KD),” “chronic pruritus,” “chronic actinic dermatitis (CAD),” “cutaneous T-cell lymphoma,” “Well’s syndrome (WS),” “keloids,” “hypertrophic scars (HTS),” “granuloma annulare (GA),” “reactive perforating collagenosis (RPC),” “lichen amyloidosis (LA),” “eosinophilic annular erythema (EAE),” “Netherton’s syndrome (NS),” “papuloerythroderma of ofuji (PEO),” “hidradenitis suppurativa(HS),” “hyperimmunoglobulin-E syndrome (HIES),” “neurofibromatosis (NF),” “IPEX syndrome,” “palmoplantar pustulosis (PPP),” “hypereosinophilic syndrome (HES),” “lamellar ichthyosis (LI),” “graft versus host disease (GVHD),” “food allergy,” and “trichothiodystrophy (TTD).” All original studies including case reports, case series, and clinical trials were included, if they were full text, involved a dermatologic condition treated by dupilumab, and published in English. Articles were excluded, if they were conference abstracts, non-clinical reports or *in vitro* studies. All references were checked and additional articles included in the study. Schematic representation of the search strategy is delineated in Figure 1.

RESULTS

Clinical uses

AD

Profitability of dupilumab in AD was first exemplified in a robust, early-phase, development program by Beck *et al.*^[7] At 12 weeks, 85% of dupilumab treated patients achieved 50% reduction of the eczema area severity index (EASI) score compared to 35% in the placebo group ($P < 0.001$). Similarly, the pruritus numeric rating scale (NRS) score reduced by 55.7% for dupilumab treated patients, compared with 15.1% for the placebo group.

A larger, dose-ranging trial of 380 patients using five dupilumab dosing schedules with one placebo, showed 300 mg weekly and biweekly dosings to be more effective than the 300 mg monthly, 200 mg biweekly, and 100 mg monthly dosing schedules; with percentage reduction of the EASI being 73.7%, 68%, 64%, 65%, and 45%, respectively.

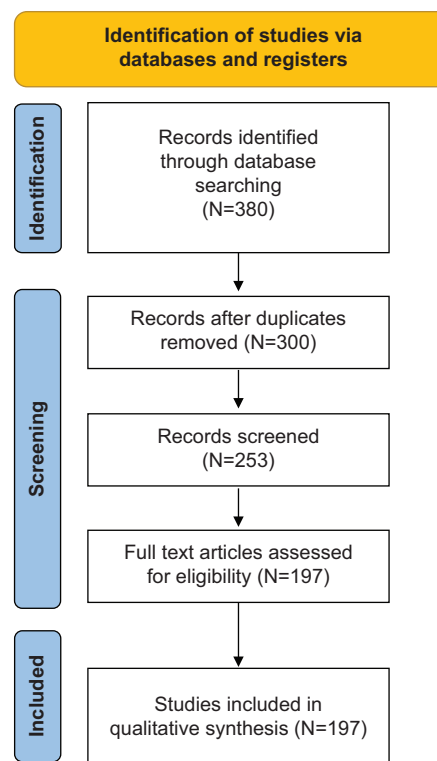


Figure 1: Schematic representation of the search strategy followed for this review.

The placebo arm on the other hand depicted reduction of the EASI score by 18.1% ($P < 0.0001$).^[8]

Dupilumab’s efficacy in AD was further corroborated by two phase III studies; SOLO-1 and SOLO-2. In both programs, 1379 adult patients with moderate-to-severe AD were randomized to receive placebo or a 600mg loading dose of dupilumab, followed by weekly or biweekly injections of dupilumab. In SOLO-1, Investigator’s Global Assessment (IGA) score of 0 or 1 with a 2-point or greater improvement was reached by 37% in the weekly cohort, and 38% in the fortnightly cohort, with EASI-75 responses being achieved by 52% and 51% in both groups, respectively. In the placebo group, IGA score was sustained by 10%, and EASI-75 response was seen in 15% of the patients. In SOLO-2, both dupilumab groups achieved a 36% IGA response, with EASI-75 responses observed in 48% of patients receiving weekly dupilumab, and 44% of patients receiving fortnightly dupilumab. The placebo group on the other hand demonstrated IGA and EASI-75 responses in 8% and 12% of patients, respectively.^[4]

An additional phase III trial, CHRONOS, analyzed concomitant topical corticosteroid (TCS) along with dupilumab versus placebo, over 52 weeks in moderate-to-severe AD. The EASI-75 response was obtained by week 16, and sustained through 1-year in 64% of patients treated with dupilumab (300 mg weekly) plus a TCS; and in 65% of

patients receiving dupilumab (300 mg fortnightly) plus a TCS. In the placebo group, the EASI-75 response at 1 year was reported in 22% of patients.^[9] Other findings revealed through this study included; fewer AD flares in both dupilumab groups (13% and 14% in those receiving it weekly and fortnightly, respectively, compared with 41% of those treated with placebo), reduction in TCS and systemic rescue therapy with 33.7% (weekly dupilumab) and 30.1% (fortnightly dupilumab) of topical and systemic medication free days versus 23.7% in the placebo group ($P < 0.0001$), statistically significant improvement in the pruritus NRS score at week 2 in the dupilumab plus TCS groups versus placebo, with improvements maintained through week 52, and parallel improvement in health-related quality of life (QoL) and least square mean reduction from baseline in the dermatology life quality index (DLQI) scores of each group, along with statistically significant benefit in both dupilumab treated groups ($P < 0.0001$).^[9]

Moreover, the safety profile of dupilumab according to these trials (SOLO-1, SOLO-2, and CHRONOS) was comparable to placebo, with discontinuation rates being lower overall for dupilumab versus placebo (3% vs. 8%, respectively).

Mechanism of action of dupilumab in AD is described in Figure 2.^[7,10] Dupilumab also significantly decreases serum levels of the chemokine CCL17, a key regulator of Th2 mediated immunity; that is a specific and objective marker of AD disease activity.^[11]

PN

PN is a chronic cutaneous disorder presenting as multiple pruritic nodules particularly involving the trunk and extensor surfaces of the extremities. In 50% of cases, an atopic predisposition is present.^[12] Although, the pathogenic mechanism underlying PN is not clearly elucidated, an emerging role of Th2 signaling is suggested. Increased expression of phosphorylated signal transducer and activator of transcription (STAT) 6, (a key transcription factor mediating Th2 signaling), as well as upregulation of interleukin (IL)-31, IL-4, and IL-13 in PN affected skin, majorly contribute toward the intense pruritus accounted in PN by activating sensory neuronal pathways following direct stimulation of Th2 inflammatory factor receptors in the sensory neurons of the dorsal root ganglia.^[13-15] Dupilumab by binding to IL-4R α (type I and II) and IL-13R α 1 receptors, antagonizes Th2 cell-mediated inflammatory responses and blocks significant abnormal interactions and dysfunction between immune cells and neuronal circuits that drive the itch-scratch cycle in PN.^[7,16]

Till date, around 120 PN patients with successful outcomes following dupilumab therapy (label dosing) in individual reports and case series have been reported and are outlined in Supplementary Table 1.^[16-36] Pruritus is generally the first

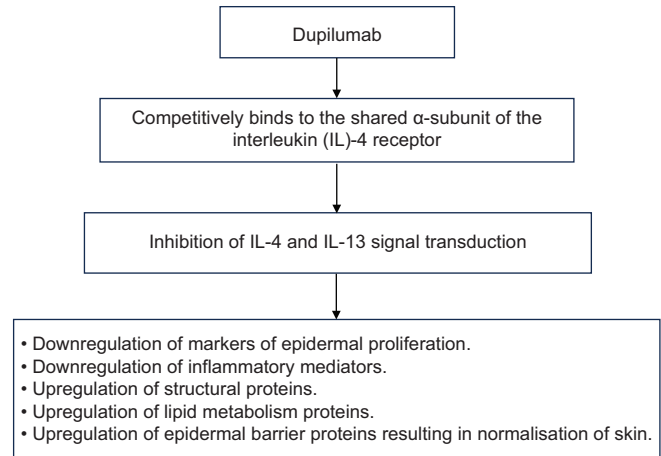


Figure 2: Mechanism of action of dupilumab in atopic dermatitis.

symptom to respond in PN, followed by nodular regression. Besides, latency periods for the reduction of pruritus and clinical manifestations of PN vary from patient to patient. Further in atopics with PN, a faster response is obtained, although final outcomes in atopics and non-atopics are similar.^[7,17]

In a systematic review by Husein-ElAhmed *et al.*,^[37] the authors concluded that following dupilumab therapy complete remission can be expected if by 8 weeks patients observe clinical improvement, and a 50% reduction of lesions on the NRS. Conversely, if amelioration of lesions occurs after 12 weeks and a 50% reduction of lesions is not achieved, obtaining a complete clinical response is unlikely.

CHE

In CHE, clinical manifestations are diverse, and pose diagnostic/therapeutic challenges. Further, the debilitating quality of CHE profoundly affects the QoL of patients.^[38] Frequent phenotypes observed include dyshidrotic (vesicular) and hyperkeratotic/fissured hand eczema, allergic contact dermatitis (ACD), and irritant contact dermatitis.^[39] As IL-4R is highly elevated in CHE skin, IL-4/IL-13 may have a role in the pathophysiology of CHE, similar to that observed in AD. This imbrication of CHE and AD transcriptomes outlines the efficacy of dupilumab in CHE.^[40] At present, utility of dupilumab in CHE has been majorly demonstrated in case reports/case series, with two prospective observational studies and one retrospective review highlighting the same [Supplementary Table 2].^[41-54]

ACD

ACD is commonly seen in patients with AD, suggesting a type IV hypersensitivity reaction, associated with defective skin barrier function. Although Th1 and Th17 cells are traditionally considered the primary effector cells in ACD, recent studies have demonstrated cytokine responses to be

haptens-specific in ACD, with additional elaboration of Th2 and Th22 responses, depending on the involved allergen.^[55] Besides, after prolonged/repeated allergen exposure in ACD, a predominant Th2 response is elicited.^[56]

The role of IL-4 in ACD has been substantiated by IL-4 knockout mice to contact allergens like oxazolone, characterized by Th2 mediated sensitization.^[57] In addition, immunochemical analysis in ACD patients have revealed IL-4 receptor α -chain immunoreactivity and >5-fold increase in IL-4 mRNA levels, thereby concluding IL-4 and IL-13 as important cytokines in ACD.^[58,59] By targeting IL-4, dupilumab can reduce symptoms in this subset of patients. Moreover, as barrier function improves in patients with AD following dupilumab therapy, patients susceptibility to allergens further reduce.^[60] Besides, even in ACD not associated with AD, dupilumab maybe effective following failed immunosuppressive therapies.^[61]

Dupilumab has been particularly beneficial in ACD secondary to fragrances, balsam of Peru, sesquiterpene lactones, nickel, glues, textile, rubber, dyes, cosmetic preservatives, and home care products.^[62-67] Further, in systemic allergic dermatitis, namely, balsam and nickel allergy syndrome, where ACD remains uncontrolled despite prudent contact allergen avoidance, dupilumab has proven to be an efficacious solution.^[68] However, even when on dupilumab, localized flares of ACD have been reported, necessitating simultaneous allergen avoidance. In addition, in patients experiencing good clinical response with dupilumab, a trial of re-exposure to contact allergens needs to be considered, and though dupilumab is effective in some cases of ACD, clinicians need to be aware that patients may not achieve complete clinical improvement, and may benefit from shorter intervals/longer duration of follow up; use of standardized assessments to monitor for clinical improvement; and continued allergen avoidance.^[69] Another point to consider is the occurrence of false-negative patch test reactions and recall dermatitis at patch test sites in patients on dupilumab for ACD. For this, repeat patch testing is warranted once dupilumab is discontinued. Moreover, patch testing in patients on dupilumab should always be interpreted with caution.^[70] At present, literature emphasizing the utility of dupilumab is limited to case reports/series with the need for randomized controlled trials (RCTs) to provide more evidence in this regard.

AA

AA is an inflammatory non-scarring alopecia commonly encountered by dermatologists. Despite its increased prevalence, therapeutic outcomes of AA remain limited. Based on the fact that AA and AD demonstrate common inflammatory signaling pathways (including Th2 overactivation; and upregulation of IL-4 and IL-13), the

role of dupilumab in AA has been proposed.^[71,72] However, antagonistic Th2 effects by dupilumab results in dysregulation (either up/downregulation) of Th1/Th17 responses, causing a cytokine shift that eventually determines whether dupilumab will precipitate or remit AA.^[73] Moreover, in patients with severe AD and AA, where massive release of interferon (IFN)- α is involved, control of AD is sufficient to allow resolution of AA with dupilumab. Conversely, in patients without pre-existing AA in AD, dupilumab therapy heralds an immune shifting that paradoxically precipitates AA, mediated by autoreactive CD8+ T-cells.^[74] In addition, it is seen that reduction in serum levels of thymus and activation-related chemokine (TARC) is associated with hair regrowth in AA, whereas elevation of TARC levels exacerbates AA following treatment with dupilumab.^[75] Furthermore, blockade of IL-4 and IL-13 by dupilumab disrupts the interleukin milieu in sebaceous glands, resulting in sebaceous gland atrophy and non-scarring alopecia,^[76] which histologically does not express features of AA, suggesting dupilumab-induced non-scarring alopecia to be an AA-like drug reaction.^[77] Interestingly, Ständer *et al.*,^[78] have postulated that dupilumab neither induces nor improves AA, with the observed association being random, due to high rates of spontaneous remission and IFN signature characterization in AA. Nevertheless, as reports exemplify both precipitation and alleviation of AA post dupilumab therapy, studying them become essential and are elaborated in Supplementary Table 3.^[73,75,76,78-90]

Chronic urticaria

Chronic urticaria is a mast cell (MC) mediated disease presenting as wheals, angioedema or both, and lasting for >6 weeks. Although current management guidelines recommend a step-wise approach, beginning with antihistamine therapy and gradually escalating its dose, some patients remain refractory to the usual treatment guidelines, that include omalizumab and cyclosporine.^[91] Dupilumab is of particular value in those chronic urticaria patients who are unresponsive to omalizumab, in both chronic spontaneous urticarial (CSU) and chronic inducible urticaria.^[92-102]

Th2 inflammation dominates urticaria pathogenesis, wherein IL-4 and IL-5 stimulate the production of IgE antibodies that subsequently bind to the Fc ϵ RI, and promote MC degranulation. Further, IL-4 augments Fc ϵ RI cell surface expression, Fc ϵ RI α -specific mRNA, and Fc ϵ RI-mediated histamine release. In addition, following long-term exposure, IL-4 alters human skin MCs by strengthening MC numbers and intensifying the processes associated with allergic inflammation. By blocking both IL-4 and IL-13, dupilumab halts the class switching of B-cell immunoglobulins toward IgE and ameliorates symptoms and signs associated with urticaria.^[97,103-105]

In two RCTs that studied the efficacy of dupilumab in CSU for omalizumab naïve patients ($n = 138$) and omalizumab intolerant/incomplete responders ($n = 108$), it was seen that in the omalizumab-naïve group, there was an 8.5 points higher reduction in the urticaria activity score over 7 days (UAS7) ($P = 0.0003$), as well as greater reduction of pruritus and wheals at week 24 (31.4% of patients), whereas in the omalizumab refractory group, the UAS7 score had reduced to zero in 13% of patients treated, and improvement in itch and hives severity demonstrated only a marginal statistical significance based on health authority hierarchy.^[106] Apart from the above RCTs, remaining data for dupilumab in chronic urticaria are limited to case reports/series [Supplementary Table 4].^[93-98,101,102]

BP

BP is the most common autoimmune subepidermal blistering disease of the skin, affecting all age groups, though most commonly encountered in the elderly.^[107] Two target antigens; BP180 and BP230 are involved in blister formation in BP. In addition, type 2 pro-inflammatory cytokines, namely, IL-4 and IL-13 have been detected in blister fluid/skin biopsies of BP patients, and increased levels of IgE and peripheral eosinophilia correlate with disease activity.^[108,109] Dupilumab in BP directly blocks IL-13 and IL-4 and indirectly downregulates IgE secretion and eosinophilic activity by inhibiting preactivated B-cell proliferation; directing human B-lymphocytes to switch to IgG4, and plummeting eosinophilic chemotaxis and Th2-associated chemokine activity without significant modulation of Th1-associated genes.^[110,111] Besides, dupilumab reduces peripheral itch sensory neuronal signaling by antagonizing IL-4, IL-13, and reducing IL-31 secretion from eosinophils and is of particular value in BP.^[112]

Dupilumab is effective in new/relapsed cases of BP, requiring at least 16–20 weeks to demonstrate disease clearance (defined as absence of both bulla and pruritus), or satisfactory response (defined as documented clinical improvement and patients desire to continue dupilumab).^[113,114] In general, within 5 weeks, the consolidation phase (time at which no new lesions have developed for a minimum of 2 weeks and approximately 80% of lesions have healed) ends, with significant improvements being witnessed after 8 weeks of treatment initiation.^[114] Pruritus is the first symptom to improve (as early as 1 week) majorly improving the patient's QoL.^[115] Furthermore, dupilumab enables amelioration of blistering and intractable pruritus in those BP patients refractory to systemic glucocorticoids, multiple immunosuppressants, omalizumab, intravenous immunoglobins (IVIG), rituximab, and plasmapheresis.^[116,117] Moreover, dupilumab can be combined with systemic glucocorticoids, azathioprine, mycophenolate mofetil (MMF), methotrexate, IVIG,

and rituximab to treat BP, enabling faster steroid taper, quicker dose reduction, and subsequent stoppage of immunosuppressants.^[107,113,114,116-119] Interestingly, Yang *et al.*,^[120] demonstrated combination of dupilumab and low-dose glucocorticoids (0.4mg/kg/day methylprednisolone) to be effective/safe in treating BP, allowing the cumulative dose of methylprednisolone to be >50% less than the conventional regimen and offering an added steroid sparing advantage.

In addition, dupilumab delineates efficacy/safety in treating immune checkpoint inhibitor (ICI)-induced BP. Of the ICIs that induce BP, dupilumab has been effective against nivolumab and pembrolizumab.^[121,122] As traditional therapies such as azathioprine and MMF are relatively contraindicated in these patients due to their concurrent malignancies, dupilumab serves as a valuable alternative due to lower rates associated with immune suppression.^[122] Cessation of new blister formation is usually evident by 1–2 months; following dupilumab treatment in these cases.^[121,122] Besides, dupilumab is safe as well as effective in elderly individuals and adolescents with refractory BP.^[107,113-119] Even so, as dupilumab has minimal immunosuppressive effects, it can be safely used in patients with tuberculosis and hepatitis C.^[115,123] In BP presently, the dose of dupilumab has not been standardized. In most patients, the AD dosing is employed. However, in patients not showing satisfactory responses, the dose can be augmented by 300 mg weekly or 600 mg every other week. This up dosing has been associated with clinical remission with no apparent adverse reactions.^[113,120]

Furthermore, dupilumab's favorable discourse has been observed in BP variants such as vesicular pemphigoid, erythrodermic pemphigoid, and pemphigoid nodularis.^[123-125] At present, the utility of dupilumab in BP is only exemplified in case reports/series, with the need of RCTs to strengthen each observation.^[107,113-120]

PG

PG is a dermatosis of pregnancy presenting in the second and third trimester. Despite spontaneous improvement during late pregnancy, relapses during the time of delivery are typical. Recurrence in successive pregnancies is frequent; occasionally having an earlier onset that may pose the risk of prematurity and growth restriction for the fetus.^[126] Due to clinical and pathogenic similarities of PG and BP, dupilumab's utility in PG is considered.

Dupilumab (label dosing) in an anecdotal report demonstrated improvement of pruritus and bullous lesions in a 30-year-old woman with PG (20 weeks of gestation), along with prednisolone. Besides, following delivery, there was no recurrence in the post-partum period, and within 3 months BP-180 antibodies had negativized. Even so, following the loading dose of dupilumab, only two maintenance doses

were sufficient to control the disease. Moreover, no untoward events were witnessed in the mother and neonate.^[127]

BPP

BPP is a clinical subtype of cicatricial pemphigoid (CP) without mucous membrane involvement; characterized clinically by subepidermal blisters, erosions, hemorrhagic crusts, and atrophic scars confined to the head, neck, and upper trunk.^[128] Dupilumab outlined favorable effects in two patients with BPP, unresponsive to conventional therapy (that included systemic steroids, MMF, methotrexate, dapsone, doxycycline, nicotinamide, and rituximab). Rapid improvement and clearance of lesions were observed after the completion of three doses of dupilumab.^[129,130] As pathogenesis in BPP comprises lymphocytosis, eosinophilia, elevated levels of basement membrane IgG, and tissue scarring/fibrosis, the role of dupilumab in BPP has been propounded.^[129]

EBP

EBP is a rare clinical subtype of autosomal dominant (or less commonly recessive) dystrophic epidermolysis bullosa (DEB). In addition to usual manifestations of DEB such as skin fragility (secondary to trauma), milia, and nail dystrophy, EBP presents with severe pruritus, prurigo-nodularis, and lichen simplex chronicus such as lesions, often complicating the clinical diagnosis.^[131] Proposed mechanism of dupilumab in EBP is blockade of IL-4R α -induced sensitization of sensory neurons to pruritogens, thereby interrupting the itch-scratch cycle, a critical component in the recovery of lesions in EBP.^[14] However, expressions of IL-4 and IL-13 in EBP remain to be investigated. Nevertheless, as dupilumab has been successful in the treatment of a variety of pruritic diseases, dupilumab maybe considered a good choice in EBP.^[132] At present, only case reports/series have elaborated the usefulness of dupilumab in EBP and are portrayed in Table 1,^[132-135] with RCTs being needed to strengthen these findings.

GD

GD is an inflammatory immune disorder presenting as flesh-colored to erythematous, edematous papules, and/or papulovesicles, commonly involving the trunk and proximal extremities of middle aged men.^[136] Apart from its idiopathic occurrence, GD has been reported following conventional chemotherapy, ICI therapy, recombinant human IL-4 therapy, and ipilumab (anti CTLA-4 monoclonal antibody) therapy.^[137-140] The pathophysiology of GD is yet to be elucidated, though some reports suggest an overexpression of IL-4 to play a role.^[141] Furthermore, with increasing age, the Th1/Th2 system is skewed toward

a Th2-inflammation profile, with enhanced non-specific B-cell activation and IgE antibody production.^[142,143] Based on these postulations, dupilumab has been employed in the treatment of GD. At present, two individual reports and a case series of three patients have elaborated dupilumab's contribution in GD.^[144-146] In all, within 12-14 weeks of dupilumab treatment, complete regression of dermatologic signs and pruritus was observed, without the occurrence of any untoward event.

HHD

HHD is an autosomal dominant genodermatosis principally characterized by flaccid blisters and malodorous erosions involving intertriginous areas, often accompanied by chronic pruritus. Mutations in the ATP2C1 gene are responsible for defective keratinocyte cell-to-cell adhesion, leading to acantholysis.^[147] Although not indicated for HHD, few reports have delineated dupilumab to be effective for the same, details of which are outlined in Table 2.^[148-151] As the mechanism of dupilumab in HHD is unclear, it is proposed that blockade of IL-4 and IL-13 may interfere with the agonistic effects of the cytokine CCL26 on CCR3, thereby preventing activation and chemotaxis of eosinophils, basophils, and Th2 lymphocytes, with subsequent inhibition of intracellular calcium release.^[152] Right now, the optimal dose and frequency of dupilumab in HHD is not known, and some patients may benefit with more frequent injections.

PV

PV is an intraepidermal immunobullous disorder targeting desmosomal adhesion proteins, desmoglein (Dsg)1, and Dsg 3.^[153] Although systemic glucocorticoids remain the first-line therapy for PV, requirement for high dosage and long-term usage often herald untoward events. Moreover, other immunosuppressive drugs such as rituximab, azathioprine, MMF, cyclophosphamide, and methotrexate are not viable options in patients with an underlying infection.

At present, the utility of dupilumab in PV has been exemplified in two case reports.^[154,155] In the first report (35-year-old male), the patient had PV along with pulmonary Kochs and was on antitubercular therapy. As an underlying sepsis was suspected, the dose of methylprednisolone (40 mg/day) could not be increased and dupilumab (label dosing) was added to the therapeutic regimen, along with antibiotics and low-dose IVIG (15 g for 4 days). The above combination resulted in regression of lesions with the pemphigus disease area index decreasing from 97 to 42 after 45 days of treatment, along with reduction of blood IgE levels and eosinophil count.^[154] The second report delineated dupilumab (label dosing) monotherapy to be effective in PV following failed treatment with systemic steroids. Within

Table 1: Reports portraying the utility of dupilumab in epidermolysis bullosa pruriginosa.

| S. No. | Authors/Year | Study type | Patient details | Previous failed therapies | Dupilumab therapy | Remarks | Adverse effects |
|--------|---|---------------------------|---|--|---|--|-----------------|
| 1. | Shehadeh <i>et al.</i> , ^[133] /2020 | Case report. | 52-year-old female with blisters and erosions since birth. | <ul style="list-style-type: none"> • Super potent TCS. • Fexofenadine. • Hydroxyzine. • Promethazine. • Medicinal cannabis. • St John's Wort. | Label dosing. | <ul style="list-style-type: none"> • At 4 weeks: Marked improvement seen. • At 12 weeks: Improvement progressed. | None. |
| 2. | Clawson <i>et al.</i> , ^[134] /2021 | Case report. | 39-year-old male with papulonodules on bilateral upper and lower limbs. | <ul style="list-style-type: none"> • TCS. • Topical calcineurin inhibitors. • Oral dapsone/cyproheptadine. | Label dosing. | <ul style="list-style-type: none"> • Complete resolution of pruritus by week 4 of dupilumab treatment. • No development of new lesions. • At 9 months there was complete relief of itching with slowly resolving skin lesions. | None. |
| 3. | Zhou <i>et al.</i> , ^[135] /2021 | Case series (2 patients). | 15-year-old male and 27-year-old female with unresponsive EBP. | <ul style="list-style-type: none"> • Systemic steroids. • Cyclosporine. • Mycophenolate mofetil. • Thalidomide. • Lenalidomide. • Omalizumab. • Tofacitinib. • Ondansetron. • N-acetylcysteine. • Gabapentin. • Pregabalin. • Naltrexone. • Melatonin. • Clonidine. • Antidepressants • Anti-histaminics. • Phototherapy. | Label dosing in one patient and 300 mg/week in another patient. | <ul style="list-style-type: none"> • Patient receiving label dosing: At 6 weeks reduction in itch from 8/10 to 4.5/10 in the ten-point itch scale. • Patient receiving 300mg weekly dose showed reduction in itch from 10/10 to 2/10 in the 10-point itch scale. | None. |
| 4. | Wang <i>et al.</i> , ^[132] /2021 | Case report. | 10-year-old female with scattered dark red papules and nodules with intense pruritus involving the lower limbs, upper limbs and trunk, with pronounced lesions over dorsa of hands and shins. | <ul style="list-style-type: none"> • TCS/Systemic CS. • Antihistamines. | Label dosing. | Within 15 days of treatment, lesions over the dorsa of hands began to flatten and itching was slightly relieved, with progressive amelioration of symptoms as therapy progressed. | None. |

EBP: Epidermolysis bullosa pruriginosa, TCS: Topical corticosteroid, CS: Corticosteroids

4 weeks, marked improvement was noticed, but as fledgeling oral lesions continued erupting within days before the next

dose, weekly dupilumab (300 mg) injections were given that resulted in healing of all lesions by 6 weeks.^[155]

Table 2: Reports highlighting the utility of dupilumab in Hailey-Hailey disease.

| S. No. | Authors/Year | Study type | Patient details | Prior failed therapies | Dupilumab therapy | Remarks | Adverse effects |
|--------|---|----------------------------|--|---|-------------------|---|-----------------|
| 1. | Alzahrani <i>et al.</i> , ^[148] /2021 | Case series of 3 patients. | <ul style="list-style-type: none"> • 2 females in their 50s. • 1 male in his 70s. | <ul style="list-style-type: none"> • Isotretinoin. • Acitretin. • Etanercept. • Prednisolone. • Oral antibiotics. • Anti-histaminics. • Naltrexone. • Cyclosporine. • Local botulinum toxin. | Label dosing. | Significant improvement was seen after an average of 2 months and sustained for 17–25 months. | None. |
| 2. | Alamon-Reig <i>et al.</i> , ^[149] /2022 | Case series of 3 patients. | <ul style="list-style-type: none"> • 2 females (56 years/59 years). • 1 male (52 years). | <ul style="list-style-type: none"> • Anti-histaminics. • Acitretin. • Systemic steroids. • Methotrexate. • Cyclosporine. • Hydroxychloroquine. • Naltrexone. • Apremilast. • Fluconazole. • Tetracycline. • Dapsone. • Oxybutynin. • Mycophenolate mofetil. • Local laser ablation. | Label dosing. | <ul style="list-style-type: none"> • 2 patients improved with treatment. • One patient did not show any improvement. | None. |
| 3. | Licata <i>et al.</i> , ^[150] /2022 | Case report. | 22-year-old female. | Cyclosporine. | Label dosing. | Resolution of lesions after 4 months of treatment. | None. |
| 4. | Brito Caldeira <i>et al.</i> , ^[151] /2023 | Case report. | 57-year-old lady. | Low dose naltrexone. | Label dosing. | <ul style="list-style-type: none"> • Pruritus and sleep quality improved drastically after the first dose. • Significant healing of skin lesions was noticeable after 12 weeks. | None. |

In acute PV, higher concentrations of serum IgE and IgG4 antibodies are seen along with IgE epidermal deposits. As Th2 cells assist formation of IgG1 and IgG4 antibodies against Dsgs, dupilumab's role in PV is postulated. By antagonizing IL-4, dupilumab affects IgE-related signaling through IL-4 on Th2 cells and ameliorates the pathogenic cascade.^[156,157] RCTs with dupilumab in PV become essential to strengthen its utility for this indication.

CONCLUSION

Although primarily used for AD, dupilumab has been found to be useful in a number of off-label dermatologic indications. Besides, with a favorable safety profile, and an established and efficient clinical use for a broad range of populations, dupilumab holds promise as a newer treatment option for a

plethora of dermatologic conditions. With numerous clinical trials ongoing, we expect dupilumab's usage in dermatology to expand in the near future.

Ethical approval

The Institutional Review Board approval is not required.

Declaration of patient consent

Patient's consent not required as there are no patients in this study.

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Conflicts of interest

There are no conflicts of interest.

Use of artificial intelligence (AI)-assisted technology for manuscript preparation

The authors confirm that there was no use of artificial intelligence (AI)-assisted technology for assisting in the writing or editing of the manuscript and no images were manipulated using AI.

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SUPPLEMENTARY TABLES

Supplementary Table 1: Reports demonstrating the efficacy of dupilumab in prurigo nodularis.

| S. No. | Authors/Year | Type of study | Patient details | History of atopy | Prior treatments | Latency period till improvement |
|--------|---|--|---|--------------------|--|-------------------------------------|
| 1. | Chiricozzi <i>et al.</i> , ^[17] /2020 | Retrospective multicentre trial on 27 patients. | <ul style="list-style-type: none"> • M:F=11:16. • Age range: 23–83 years. | Yes (18) No (9) | <ul style="list-style-type: none"> • Systemic CS. • Cyclosporine. • Phototherapy. • Methotrexate. • Azathioprine. | 4 weeks for both itch and nodules. |
| 2. | Calugareanu <i>et al.</i> , ^[16] /2020 | Retrospective study on 16 patients. | <ul style="list-style-type: none"> • M:F=7:9 • Age: 56 years (median) | Yes (7) No (9) | <ul style="list-style-type: none"> • TCS. • Phototherapy. • Methotrexate. • Cyclosporine. • Thalidomide. • Antihistamines. • Dapsone. • Retinoids. • MMF. • Azathioprine. • Nemolizumab. • Anti-IL-17 and TNFα agents. | 3 months for both itch and nodules. |
| 3. | Ferrucci <i>et al.</i> , ^[18] /2021 | Retrospective observational cohort study on 11 patients. | <ul style="list-style-type: none"> • M:F=6:5 • Age Range: 19–88 years. | Yes | <ul style="list-style-type: none"> • TCS. • Topical Calcineurin antagonists. • Antihistamines. • Systemic CS. • Cyclosporine. • Methotrexate. | 4 weeks for both itch and nodules. |
| 4. | Tilotta <i>et al.</i> , ^[19] /2021 | Case series of 11 patients. | <ul style="list-style-type: none"> • M:F=7:4. • Age range: 62–78 years. | Yes | <ul style="list-style-type: none"> • TCS. • Antihistamines. • Systemic CS. • Cyclosporine. | 4 weeks for both itch and nodules. |
| 5. | Napolitano <i>et al.</i> , ^[20] /2020 | Case series of 9 patients. | <ul style="list-style-type: none"> • 9 males. • Age range: 31–63 years. | Yes | <ul style="list-style-type: none"> • TCS. • Antihistamines. • Phototherapy. • Cyclosporine. • Methotrexate. | 16 weeks for both itch and nodules. |
| 6. | Tavecchio <i>et al.</i> , ^[21] /2020 | Case series of 18 patients. | Age and gender not specified. | Yes | <ul style="list-style-type: none"> • TCS. • Topical Calcineurin antagonists. • Systemic CS. • Cyclosporine. • Azathioprine. • Methotrexate | 4 weeks for both itch and nodules. |
| 7. | Reynolds <i>et al.</i> , ^[22] /2020 | Case series of 4 patients. | <ul style="list-style-type: none"> • M:F=1:3. • Age range: 17–71 years. | Not specified. | <ul style="list-style-type: none"> • Topical/intralesional steroids. • Topical calcineurin blockers. • Topical crisaborole. • Systemic CS. • Antihistamines. • Doxycycline. • Methotrexate. • Gabapentin. | 4 weeks for both itch and nodules. |

(Contd...)

Supplementary Table 1: (Continued).

| S. No. | Authors/Year | Type of study | Patient details | History of atopy | Prior treatments | Latency period till improvement |
|--------|---|----------------------------|---|------------------|---|--|
| 8. | Beck <i>et al.</i> , ^[23] /2019 | Case series of 3 patients. | <ul style="list-style-type: none"> • M:F=2:1. • Age range: 50–70 years. | Not specified. | <ul style="list-style-type: none"> • Systemic CS. • Antihistamines. • Doxepin. • Gabapentin. • Phototherapy. • Cryotherapy. • Mupirocin. • Cyclosporine. • Dronabinol. | 4–12 weeks for both itch and nodules. |
| 9. | Holm <i>et al.</i> , ^[24] /2020 | Case series of 3 patients. | <ul style="list-style-type: none"> • Age range: 42–57 years. • All females. | No | <ul style="list-style-type: none"> • TCS. • Topical calcineurin inhibitors. • Phototherapy. • Cannabinol. • Antihistamines. • Systemic CS. • Methotrexate. • Azathioprine. • Tetracycline. • Metronidazole. • Thalidomide. | Not specified. |
| 10. | Almustafa <i>et al.</i> , ^[25] /2019 | Case series of 3 patients. | <ul style="list-style-type: none"> • M:F=2:1. • Age range: 41–52 years. | Yes | <ul style="list-style-type: none"> • TCS/intralesional steroids. • Topical calcineurin inhibitors. • Antihistamines. • Phototherapy. • Gabapentin. • Pregabalin. • Cyclosporine. | 2–8 weeks for itch followed by nodules. |
| 11. | Calugareanu <i>et al.</i> , ^[26] /2019 | Case report. | 30-year-old female. | Yes | <ul style="list-style-type: none"> • Cyclosporine. • TCS. • Cryotherapy. • Antihistamines. • Phototherapy. • Dapsone. • Methotrexate. • Thalidomide. | 3 months (itch and nodules). |
| 12. | Mitsuyama and Higuchi ^[27] /2023 | Case series of 4 patients. | <ul style="list-style-type: none"> • M:F=3:1. • Age range: 65–84 years. | Yes | <ul style="list-style-type: none"> • Cyclosporine. • TCS. • Phototherapy. • Antihistamines. • Systemic CS. • Cyclosporine. | 2–4 weeks (itch) 4–8 weeks (nodules). |
| 13. | Giura <i>et al.</i> , ^[28] /2020 | Case report. | 85-year-old female. | No | <ul style="list-style-type: none"> • TCS and systemic CS. | 1 week (itch) 4 weeks (nodules). |
| 14. | Romano ^[29] /2021 | Case report. | 61-year-old female. | No | <ul style="list-style-type: none"> • Not specified. | 4 weeks for both itch and nodules. |
| 15. | Bloomsteain and Hawkes ^[30] /2021 | Case report. | 76-year-old man. | Yes | <ul style="list-style-type: none"> • TCS. • Antihistamines. | 4 weeks for both itch and nodules. |
| 16. | Criado <i>et al.</i> , ^[31] /2020 | Case report. | 87-year-old male. | Yes | <ul style="list-style-type: none"> • Systemic CS. • Antihistamines. • Cyclosporine. • Methotrexate. • Pregabalin. • Mirtazapine. | 4 weeks for itch and 16 weeks for nodules. |

(Contd...)

Supplementary Table 1: (Continued).

| S. No. | Authors/Year | Type of study | Patient details | History of atopy | Prior treatments | Latency period till improvement |
|--------|---|----------------------------|---|------------------|---|--|
| 17. | Tanis <i>et al.</i> ^[32] /2019 | Case report. | 43-year-old female. | Not specified. | <ul style="list-style-type: none"> • TCS. • Cyclosporine. • Phototherapy. • Methotrexate. | 8 weeks for both itch and nodules. |
| 18. | Fachler <i>et al.</i> , ^[33] /2021 | Case report. | 9-year-old female. | No | <ul style="list-style-type: none"> • TCS. • Antihistamines. • Phototherapy. • Cyclosporine. • Methotrexate. | 2 weeks for itch and 4 weeks for nodules. |
| 19. | Liu <i>et al.</i> , ^[34] /2021 | Case report. | 85-year-old man. | No | <ul style="list-style-type: none"> • TCS. • Gabapentin. • Thalidomide. • Ketotifen. • Cetirizine. | 12 weeks for both itch and nodules. |
| 20. | Wieser <i>et al.</i> , ^[35] /2020 | Case series of 3 patients. | <ul style="list-style-type: none"> • M:F=1:2. • Age range: 65 and 66 years. | No | <ul style="list-style-type: none"> • TCS/intralesional steroids. • Topical calcineurin inhibitors. • Systemic CS. • Methotrexate. • Antihistamines. • Gabapentin. • Phototherapy. | 4–28 weeks for both itch and nodules. |
| 21. | Kovács <i>et al.</i> , ^[36] /2020 | Case report. | 80-year-old female. | Yes | <ul style="list-style-type: none"> • TCS. • Topical calcineurin inhibitors. • Mirtazapine. • Methotrexate. • Antihistamines. • Gabapentin. • Phototherapy. • Paroxetine. • Cyclosporine. • Naloxone. • Naltrexone. | 2 weeks for itch and 10 weeks for nodules. |

TCS: Topical corticosteroid, CS: Corticosteroids

Supplementary Table 2: Reports elucidating the efficacy of dupilumab in chronic hand eczema.

| S. No. | Author/Year | Study type | Patient details | Hand eczema type/duration | History of Atopy | Prior treatment | Response to dupilumab | Adverse effects |
|--------|---|-------------|--------------------|---------------------------|------------------|--|--|-----------------|
| 1. | Weins <i>et al.</i> , ^[41] /2019 | Case report | 12-year-old male | DE/6 months | Yes | <ul style="list-style-type: none"> • TCS. • Topical antimicrobials. • Phototherapy. • Systemic prednisolone, Mtx, CsA, antimicrobials. | Complete stable remission in 4 months. | None |
| 2. | Gan <i>et al.</i> , ^[42] /2022 | Case report | 29-year-old female | Occupational CHE/5 years | No | <ul style="list-style-type: none"> • TCS • Pimecrolimus • Systemic H1 blockers. | <ul style="list-style-type: none"> • Improved in 4 weeks. • Almost healed by 16 weeks. | None |

(Contd...)

Supplementary Table 2: (Continued).

| S. No. | Author/Year | Study type | Patient details | Hand eczema type/duration | History of Atopy | Prior treatment | Response to dupilumab | Adverse effects |
|--------|---|----------------------------|---|--|------------------|---|---|--|
| 3. | Zhu <i>et al.</i> , ^[43] /2020 | Case report | 43-year-old male | Chronic irritant hand dermatitis >10 years | No | TCS and systemic CS. | Improved by 1 month and cleared by 5 years. | None |
| 4. | Nanda <i>et al.</i> , ^[44] /2019 | Case Report | 44-year-old female | DE >2 years | Yes | Antibiotics and systemic CS. | Pain disappeared by 6 weeks and lesions cleared within 8 weeks. | <ul style="list-style-type: none"> • Injection site pain. • Pruritic conjunctivitis. |
| 5. | Oosterhaven <i>et al.</i> , ^[45] /2018 | Case Report | 50-year-old female | Chronic atopic hand eczema for 9–≥35 years | Yes | <ul style="list-style-type: none"> • Emollients. • Potent TCS. • PUVA. • Alitretinoin. • CsA. • Azathioprine. • Mtx. • Systemic CS. • MPA. • Tacrolimus. | Almost clear at 16 weeks. | None |
| 6. | Halling <i>et al.</i> , ^[46] /2020 | Case Report | 67-year-old male | Vesicular hand eczema ≥2.5 years | No | <ul style="list-style-type: none"> • Potent TCS. • Coal tar. • Condy compresses. • NB-UVB. • Mtx. • Azathioprine. • CsA. • Systemic CS. | Improved in 2 weeks and cleared by 4 weeks. | None |
| 7. | Zirwas <i>et al.</i> , ^[47] /2018 | Case series of 3 patients | 2 females (65, 72 years) 1 male (48 years) | Hand eczema without atopic dermatitis | No | <ul style="list-style-type: none"> • Potent TCS and tacrolimus. • Systemic CS. • Thalidomide. • Mtx. • MMF. • CsA. • Apremilast. • Ustekinumab. | Clearance observed by 6 weeks in 2 patients. In another patient, 80% improvement seen by 3 months. | None |
| 8. | Gall <i>et al.</i> , ^[48] /2021 | Case series of 2 patients | 2 males of age 38 years. | DE for >5 years | No | <ul style="list-style-type: none"> • TCS. • Phototherapy. • Systemic CS. • Acitretin. • Apremilast. | Improved by 1–6 weeks. | None |
| 9. | Weston <i>et al.</i> , ^[49] /2018 | Case series of 2 patients. | 2 males of 37 years and 63 years. | <ul style="list-style-type: none"> • DE ≥11 years in one patient. • In the other details were not available. | Yes | <ul style="list-style-type: none"> • Highly potent TCS. • Emollients. • NB-UVB. • PUVB. • Excimer lasers. • Systemic CS. • Apremilast. • Mtx. • Efalizumab. • Etanercept. • Adalimumab. • Ixekizumab. | <ul style="list-style-type: none"> • Improved by 8 weeks. • Completely free of disease by 4 months. | None |

(Contd...)

Supplementary Table 2: (Continued).

| S. No. | Author/Year | Study type | Patient details | Hand eczema type/duration | History of Atopy | Prior treatment | Response to dupilumab | Adverse effects |
|--------|---|---|---|---|------------------|--|--|---|
| 10. | Loman <i>et al.</i> , [50]/2021 | Case series of 3 patients. | 3 males of age ranging from 47– 65 years. | Hyperkeratotic hand eczema | No | <ul style="list-style-type: none"> • Ultrapotent TCS. • Mtx. • Alitretinoin. • Acitretin. • CsA. • Azathioprine. | <ul style="list-style-type: none"> • In 2 patients lesions cleared by 16 weeks. • In one patient minimal improvement at week 16. | None |
| 11. | Waldman <i>et al.</i> , ^[51] /2020 | Case series of 15 patients | 10 males nad 5 females with mean age of 50 years. Range: 32–76 years. | DE. | No | <ul style="list-style-type: none"> • TCS. • Immunosuppressives. • Phototherapy. • Biologic drugs used in psoriasis. | <ul style="list-style-type: none"> • In 40% of patients complete clearance. • Partial response in others. | <ul style="list-style-type: none"> • Facial redness in 2 patients. • Ocular surface disease in 1 patient. |
| 12. | Oosterhaven <i>et al.</i> , ^[52] /2019 | Prospective observational study in 47 patients. | 32 males/15 females Age range: 20–69 yearss. | <ul style="list-style-type: none"> • 35 patients had chronic fissured hand eczema and 12 patients had recurrent vesicular hand dermatitis. | Yes | <ul style="list-style-type: none"> • Prednisolone. • CsA. • Mtx. • Azathioprine. • Alitretinoin • MMF. • MPA. • Tacrolimus. | <ul style="list-style-type: none"> • At 16 weeks: HESCI 50: In 87% of patients; HECSI 75: In 60% of patients; and HECSI 90: In 32% of patients. | None |
| 13. | Voorberg <i>et al.</i> , ^[53] /2022 | Prospective observational study on 72 patients. | 48 males and 24 females. Mean age 45.2±13.0 years. | 50 patients had chronic fissured hand eczema and 22 had recurrent vesicular hand disease. | Yes | <ul style="list-style-type: none"> • Prednisolone. • CsA. • Mtx. • Azathioprine. • Alitretinoin. • MPA. • MMF. • Tacrolimus. | <ul style="list-style-type: none"> • At 52 weeks: HECSI 75: In 87.1% of patients and HECSI 90: In 62.9% of patients. | Conjunctivitis, multiple filiform warts and blood eosinophilia. |
| 14. | Lee <i>et al.</i> , ^[54] /2019 | Retrospective review of 38 patients. | 15 males and 23 females. Mean age: 42.2±18.4 years. | Presentations observed were DE and contact dermatitis | Yes | <ul style="list-style-type: none"> • Prednisolone. • CsA. • MMF. | <ul style="list-style-type: none"> • At 4 months: Pruritus improved in 96.7% patients. • Pain improved in all patients. • Fissuring improved in 28.9% patients. | None |

TCS: Topical corticosteroid, CS: Corticosteroids, DE: Dyshidrotic eczema, Mtx: Methotrexate, CsA: Cyclosporine, MPA: Mycophenolic acid, MMF: Mycophenolate mofetil, NV-UVB: Narrow-band ultraviolet-B, HECSI: Hand eczema severity index

Supplementary Table 3: Summary of reports describing dupilumab's ability to remit and precipitate alopecia areata.

| S. No. | Authors/Year | Type of study | Patient Details | Presence of coexistent atopic dermatitis | Previous treatments | Dupilumab therapy | Remarks |
|--------|--|---------------------------|---|--|--|---|--|
| 1. | Alotaibi <i>et al.</i> , ^[79] /2022 | Case report | 21-year-old female with AU | Yes | <ul style="list-style-type: none"> • UVB phototherapy. • Tofacitinib. | 300 mg SC given every 2 weeks (q2w) | <ul style="list-style-type: none"> • By 2 months hair regrowth was seen on the scalp, eyebrows and eye lashes. • Only one bald patch remained at 4 months. |
| 2. | Kulkarni <i>et al.</i> , ^[73] /2022 | Case report | 16-year-old male with AT | Yes | NA | 600 mg SC loading dose, followed by 300 mg q2w (label dosing) | <ul style="list-style-type: none"> • Within 8 months of starting dupilumab, patient had almost complete hair regrowth. |
| 3. | Szekely <i>et al.</i> , ^[80] /2021 | Case report | 30-year-old male with AT | Yes | <ul style="list-style-type: none"> • TCS/Systemic CS. • Phototherapy. • Mtx. • CsA. | Label dosing | <ul style="list-style-type: none"> • Complete re-growth of hair within 3 months. |
| 4. | Babino <i>et al.</i> , ^[81] /2020 | Case report | 68-year-old female with AT | No | <ul style="list-style-type: none"> • TCS/Systemic CS. • Photodynamic therapy. • Squaric acid dibutyl ester. • CsA. | Label dosing | <ul style="list-style-type: none"> • Complete regrowth of hair within 3 months. |
| 5. | Flanagan <i>et al.</i> , ^[82] /2022 | Case report | 28-year-old female with AT | Yes | <ul style="list-style-type: none"> • TCS. • Phototherapy. | Label dosing | <ul style="list-style-type: none"> • Nearly complete regrowth of hair at 2-3 months. |
| 6. | Cho <i>et al.</i> , ^[83] /2021 | Case series of 6 patients | 3 males and 3 females with AA. Age range: 7-12 years. | Yes | <ul style="list-style-type: none"> • TCS/Systemic CS. • Topical/oral minoxidil. • Topical tacrolimus. | Label dosing | <ul style="list-style-type: none"> • 4 patients had complete regrowth. • 1 patient had 73% improvement in the severity of alopecia tool score. • 1 patient did not have any hair growth despite being on dupilumab for 16 months. |
| 7. | Fukuyama <i>et al.</i> , ^[75] /2023 | Case series of 4 patients | <ul style="list-style-type: none"> • 4 females • Age range (40-54 years) • 3 had patchy alopecic lesions. • Fourth patient had no alopecia. | Yes | <ul style="list-style-type: none"> • Intralesional CS (with minimal response). | Label dosing | <ul style="list-style-type: none"> • The 3 patients with alopecia demonstrated full hair growth within 3 months of dupilumab therapy. • In patient 4, within 8 months of dupilumab therapy, acute and diffuse hair loss was seen that progressed to total hair loss. |

(Contd...)

Supplementary Table 3: (Continued).

| S. No. | Authors/Year | Type of study | Patient Details | Presence of coexistent atopic dermatitis | Previous treatments | Dupilumab therapy | Remarks |
|--------|--|---------------------------|--|--|--|-------------------|---|
| 8. | Ludriksone <i>et al.</i> , ^[84] /2019 | Case series of 2 patients | 2 males of ages 38 and 32 years, with AA. | Yes | <ul style="list-style-type: none"> • Phototherapy. • Azathioprine. • CsA. | Label Dosing | <ul style="list-style-type: none"> • Complete hair regrowth at week 21 and 22. |
| 9. | Harada <i>et al.</i> , ^[85] /2020 | Case series of 7 patients | 5 males and 2 females. Age range: 33-52 years. | Yes | <ul style="list-style-type: none"> • TCS/Systemic CS. • Diphenylcyclopropenone. • Squaric acid dibutylester. • Phototherapy. | Label dosing | <ul style="list-style-type: none"> • Complete regrowth in 2 patients. • Partial response in 4 patients. • No response in 1 patient. |
| 10. | Ständer <i>et al.</i> , ^[78] /2020 | Case report | 53-year of male with recurrent AD. | - | - | Label dosing | <ul style="list-style-type: none"> • After 1 year of treatment with dupilumab AA developed. |
| 11. | Kanda <i>et al.</i> , ^[86] /2019 | Case report | 35-year-old male with AD | - | - | Label dosing | <ul style="list-style-type: none"> • Development of AA following 6 weeks of dupilumab therapy involving 23% of whole scalp. • Methylprednisolone pulse was simultaneously instituted with 78% reduction of AA after 4 months. |
| 12. | Flanagan <i>et al.</i> , ^[76] /2019 | Case report | 27-year-old male with AD | - | - | Label dosing | <ul style="list-style-type: none"> • Ill-defined areas of non-scarring alopecia was seen over the scalp after 18 weeks of dupilumab therapy. • This was reversed 8 weeks after discontinuation of dupilumab. |
| 13. | Gallo <i>et al.</i> , ^[87] /2020 | Case report | 24-year-old male with AD | - | - | Label dosing | <ul style="list-style-type: none"> • After 8 weeks of starting dupilumab, abrupt shedding of scalp hair was noted with a SALT score of 71.6. • Following 3 months of dupilumab discontinuation, hair regrowth was complete. |

(Contd...)

Supplementary Table 3: (Continued).

| S. No. | Authors/Year | Type of study | Patient Details | Presence of coexistent atopic dermatitis | Previous treatments | Dupilumab therapy | Remarks |
|--------|--|-------------------------------------|---|--|---------------------|-------------------|---|
| 14. | Mitchell and Levit ^[88] /2018 | Case report | 29-year-old male with AD | - | - | Label dosing | <ul style="list-style-type: none"> • Development of AA on the posterior scalp 5 weeks after starting dupilumab. • Dupilumab was not discontinued. • Intralesional triamcinolone acetonide (5mg/ml) was administered every 4 weekly with gradual improvement of AA. |
| 15. | Barroso-García <i>et al.</i> , ^[89] /2018 | Case report | 31-year-old male with severe AD | - | - | Label dosing | <ul style="list-style-type: none"> • Patches of hair loss involving the anterior scalp 6 weeks after initiation of dupilumab therapy was seen. • Dupilumab was continued along with intralesional triamcinolone acetonide on the alopecic patches. • Results of amelioration of AA with intralesional steroids was not reported. |
| 16. | Guttman-Yassky <i>et al.</i> , ^[90] /2022 | Randomized placebo-controlled trial | <ul style="list-style-type: none"> • Dupilumab group (40 patients) • Placebo group (20 patients). | In 42.5% of the study subjects. | - | Label dosing | <ul style="list-style-type: none"> • 30% improvement in SALT score at week 48 in 32.5% vs. 20%. ($P=0.067$). • 50% improvement in SALT score at week 48 in 22.5% vs. 15%. ($P=0.02$). |

AU: Alopecia universalis, AT: Alopecia totalis, AD: Atopic dermatitis, UVB: Ultraviolet-B, NA: Not available, CsA: Cyclosporine, TCS: Topical corticosteroid, CS: Corticosteroids, SALT: Severity of alopecia tool

Supplementary Table 4: Reports outlining the utility of dupilumab in chronic urticaria.

| S. No. | Authors/Year | Type of study | Study details | Remarks |
|--------|--|---------------|---|---|
| 1. | Ferrucci <i>et al.</i> , ^[93] /2020 | Case report. | <ul style="list-style-type: none"> • 28-year-old man with chronic cold urticaria who also had AD from infancy. • Prior failed treatments included prednisolone, cyclosporine and omalizumab. • Dupilumab (label dosing) started. | <ul style="list-style-type: none"> • Within 1 month of therapy • EASI score reduced by 85%. • DLQI plummeted to 0 from 12. • Ice cube test became negative. • Besides, prolonged exposure to low temperatures did not cause any problems. |
| 2. | Sun <i>et al.</i> , ^[94] /2022 | Case report. | <ul style="list-style-type: none"> • 44-year-old male with chronic urticaria and angioedema unresponsive to anti-histamines, cyclosporine omalizumab and phototherapy. • Dupilumab (label dosing) started. | <ul style="list-style-type: none"> • After the first dose of dupilumab the UAS7 score reduced to 0 from 42. • On subsequent laboratory investigation IgE levels normalised. • His condition remained stable for the next 24 months while on dupilumab maintenance therapy. |
| 3. | Goodman and Jariwala ^[95] /2021 | Case report. | <ul style="list-style-type: none"> • 18-year-old man with adrenergic urticaria with associated postural orthostatic tachycardia syndrome. • Lesions were triggered by heat, stress and exercise. • Lesions were refractory to antihistamines, leukotriene antagonists, dapsone and omalizumab. • Dupilumab (300 mg) monthly injections were started, along with propranol 20mg twice daily and an antihistaminic. | <ul style="list-style-type: none"> • Patient had good control of symptoms initially. • However, during summer, lesions exacerbated, that was controlled with dupilumab and escalated dosing propranolol (60 mg twice daily). |
| 4. | Zhu <i>et al.</i> , ^[96] /2022 | Case report. | <ul style="list-style-type: none"> • A 31-year-old male with 3-year history of CSU with no angioedema or systemic symptoms. • Patient was unresponsive to antihistaminics and omalizumab. • Dupilumab 600mg (first dose) followed by 300mg at weeks 3, 6, 10, 16 and 24 was given. | <ul style="list-style-type: none"> • Within 2 weeks of dupilumab therapy, his wheals and pruritus significantly improved and after 4 months lesions had completely disappeared. • Owing to eosinophilia following dupilumab, it was stopped and prednisolone 60 mg/day with gradual taper began. • Even 16 weeks after stopping dupilumab, remission was maintained. |
| 5. | Sirifo <i>et al.</i> , ^[97] /2022 | Case report. | <ul style="list-style-type: none"> • A 26-year-old male with cholinergic urticaria for 3 years and no history of atopy. • Lesions unresponsive to antihistamines, prednisolone, leukotriene antagonists and omalizumab. • Dupilumab (label dosing) initiated along with rupatadine 10 mg (Q6H) that was tapered and discontinued after 2 months of treatment. | <ul style="list-style-type: none"> • After 2 doses of dupilumab, patient ceased to have episodes of cholinergic urticaria and there was marked improvement in patient's quality of life. |
| 6. | Puxkandl <i>et al.</i> , ^[98] /2023 | Case report. | <ul style="list-style-type: none"> • 68-year-old woman with CSU and angioedema unresponsive to antihistamines, prednisolone and omalizumab. • Dupilumab (label dosing) along with antihistamines. | <ul style="list-style-type: none"> • After the third injection of dupilumab, patient was symptom free. |

(Contd...)

Supplementary Table 4: (Continued).

| S. No. | Authors/Year | Type of study | Study details | Remarks |
|--------|--|----------------------------|---|--|
| 7. | Lee and Simpson ^[101] /2019 | Case series of 6 patients. | <ul style="list-style-type: none">• 3 males and 3 females (average age of 36 years) refractory to antihistamines and omalizumab (300–600 mg monthly).• Dupilumab (label dosing) started. | <ul style="list-style-type: none">• Of the 6 patients:• 5 responded to dupilumab monotherapy within 3 months.• One responded with combination of dupilumab and omalizumab.• Of the responders, in 4 the UAS7 remained 0 at 14–22 months of follow up since treatment discontinuation. |
| 8. | Marchal and Reguiat ^[102] /2023 | Case report. | <ul style="list-style-type: none">• A 38-year-old woman with refractory cold urticaria evolving since 12 years and lack of therapeutic response with antihistamines and omalizumab (with even 300 mg fortnightly dosage.)• Dupilumab (label dosing) given for uncontrolled symptoms. | <ul style="list-style-type: none">• Rapid complete disappearance of her symptoms following dupilumab treatment without any flare up during cold exposure.• Even after 18 months with dupilumab maintenance, patient was in complete remission.• No side effects were encountered. |

EASI: Eczema area severity index, AD: Atopic dermatitis, DLQI: Dermatology life quality index, IgE: Immunoglobulin E, CSU: Chronic spontaneous urticarial, UAS7: Urticaria activity score over 7 days