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Review Article

Treatment of Dystrophic Epidermolysis Bullosa Pruriginosa: A Systematic Review of Clinical Outcomes after Initiation of Dupilumab Therapy

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Dystrophic epidermolysis bullosa pruriginosa (DEB-Pr), a highly pruritic subtype of dystrophic epidermolysis bullosa (DEB), can substantially impact patients' quality of life due to symptom severity. This review features 10 patients diagnosed with DEB-Pr and a history of insufficient symptom relief following anti-inflammatory treatment. However, after initiation of dupilumab therapy, these patients exhibited marked clinical improvements in pruritic and cutaneous symptoms. Interestingly, one study showed an increase in type VII collagen following dupilumab therapy. These findings highlight the influence of T helper 2 (Th2)-mediated immunity in the pathogenesis of itch in DEB-Pr and dupilumab's potential in the treatment of refractory pruritus.

1. Introduction

Dystrophic epidermolysis bullosa pruriginosa (DEB-Pr), a subtype of dystrophic epidermolysis bullosa (DEB), is characterized by nodular prurigo-like lesions with intense pruritus, along with typical DEB symptoms such as vesiculation and nail dystrophy [1]. The underlying pathophysiology responsible for pruritus in DEB-Pr remains unknown, but interleukin (IL) imbalance is believed to play a pivotal role [2]. Dupilumab, a human monoclonal antibody that binds to the IL-4 receptor alpha chain, has been investigated as a potential therapeutic option for DEB-Pr due to its ability to reduce pruritus by blocking IL-4 and IL-13 signaling pathways [1]. We systematically reviewed the literature to qualitatively assess the efficacy of dupilumab in treating itch for patients with DEB-Pr.

2. Methods

To ensure a comprehensive review, a PRISMA-guided search was conducted. PubMed (MEDLINE), Embase, Cochrane (CENTRAL), ClinicalTrials.gov, and the World Health Organization International Clinical Trials Registry Platform (WHO-ICTRP) were searched from database inception through February 13, 2023. Keywords searched included "epidermolysis bullosa" and "dupilumab" or "DUPIXENT."

Two independent, blind reviewers (CI and AH) conducted screening, citation searching, and data extraction, with any discrepancy being resolved by the senior author (PL). Full-text, English language studies investigating dupilumab for treating itch in DEB-Pr patients of all ages and sexes were included. Reviews (systematic, literature,

scoping, or narrative), patient diagnoses other than DEB-Pr, treatments other than dupilumab, outcomes excluding pruritus, duplicates, or clinical trials with incomplete or unavailable outcomes were excluded. Rayyan (Boston, MA) was used for screening and deduplication. Publication bias was addressed by searching the preprint server medRxiv.org following the above eligibility criteria. Corresponding authors were contacted for retrieval of missing data.

3. Results

The literature search yielded 69 studies, of which 7 were included (Figure 1). The total number of subjects amounted to 10 (age range, 7–52 years), with dupilumab treatment duration ranging from 12 weeks to 22 months (Tables 1 and 2) [3–9]. All subjects received a dupilumab loading dose of 600 mg [3–9]. Eight subjects received a maintenance dose of 300 mg every 2 weeks; however, one subject had inadequate symptom relief and required an increase in frequency to 300 mg weekly [3–6, 8, 9]. The two remaining subjects received a maintenance dose of 300 mg every 4 weeks [7]. Three studies [5, 7, 8] recorded baseline immunoglobulin E (IgE) levels, and two studies [5, 7] recorded baseline eosinophil levels (Table 2).

Eight subjects from six studies reported a quantitative itch score before and after dupilumab treatment (duration ranging from 12 weeks to 18 months), with an average decrease of 62.27% in itch severity [3, 5–9]. Clawson et al. provided a qualitative measurement for itch severity, reporting a substantial decrease from severe to almost complete resolution of itch after four weeks of dupilumab treatment [4]. Dermatology Life Quality Index (DLQI) was noted by Shehadeh et al., Wang et al., and Yu et al., reporting a 65.22%, 69.23%, and 100.00% decrease after 12 weeks, 7 months, and 16 weeks of dupilumab treatment, respectively [5, 6, 8]. Wu et al. reported an average decrease of 38.67% in the Children's Dermatology Life Quality Index (CDLQI) following 20 weeks of dupilumab therapy [7]. In addition, Zhou et al. reported sleep improvement in both subjects after 12 and 18 months of dupilumab treatment (Table 2) [9].

Other notable findings regarding dupilumab's effects on disease severity were reported. Shehadeh et al. and Wu et al. reported a decrease in the Epidermolysis Bullosa Disease Activity and Scarring Index (EBDASI) by 13.56% and 15.42% (average value) after 12 and 20 weeks of dupilumab treatment, respectively [5, 7]. Wu et al. also noted an average decrease in total serum IgE levels, eosinophil levels, and T helper 2 (Th2) cell levels by 76.10%, 50.34%, and 28.04%, respectively [7]. Conversely, Wu et al. showed an average increase in T helper 1 (Th1) and T helper 17 (Th17) cell levels by 38.43% and 186.49%, respectively [7]. Interestingly, Wu et al. reported an increase in type VII collagen (C7) deposition in the basement membrane of both subjects following dupilumab therapy (Table 2) [7].

All subjects noted physical exam improvements including a reduction in erythema, nodules, blisters, crusts, scales, and plaques [3–9]. No adverse effects were reported across all studies (Table 2) [3–9].

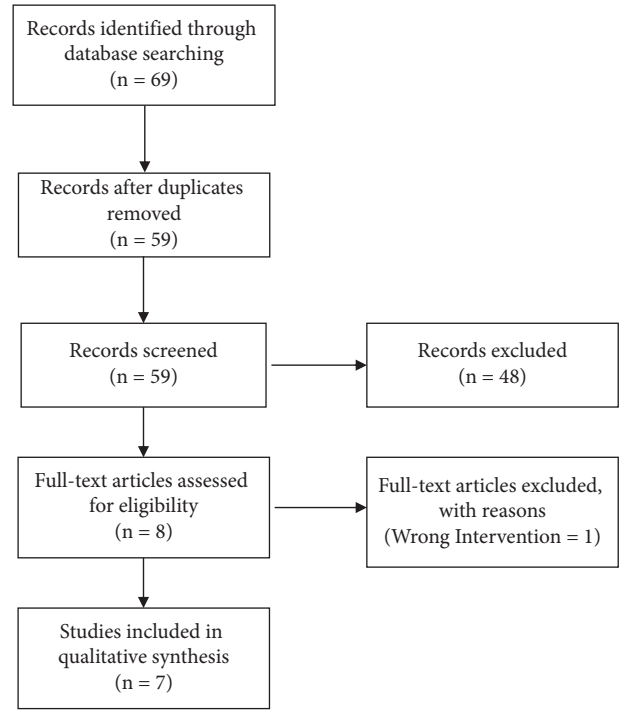

Figure 1: PRISMA flow diagram.

4. Discussion

Severe pruritus is a burdensome manifestation of DEB-Pr, leading to substantial adverse psychosocial effects [2]. The pathophysiological mechanism of intractable pruritus underlying DEB-Pr remains unknown; however, rapid improvement of symptoms with anti-inflammatory treatments has supported the role of inflammation [10]. The recalcitrant nature of DEB-Pr has led to the exploration of numerous therapeutic modalities. Anti-inflammatory agents such as corticosteroids, cyclosporine, or topical tacrolimus have demonstrated some success, but select patients with refractory symptoms persist [10]. Additional literature has highlighted the efficacy of Janus kinase (JAK) inhibitors in treating pruritic and cutaneous symptoms, but studies remain limited [1, 11, 12]. Our review includes DEB-Pr patients with a prior history of failed anti-inflammatory treatments who later illustrate marked clinical improvement in pruritus, quality of life, and cutaneous symptoms following dupilumab treatment [3–9].

Dupilumab's efficacy highlights the importance of the potential interplay between IL-4 and IL-13 pathways in the pathophysiology of itch in DEB-Pr. Moreover, studies have implicated the role of Th2-mediated immunity in the development of pruritus in DEB-Pr, supporting the possible benefits of targeted immunotherapy [13]. Supportively, Wu et al. reported decreased IgE, eosinophils, and Th2 cell levels following dupilumab treatment in both patients, with a concurrent decrease in pruritic symptoms [7]. Preliminary research has also shown clinical benefits in the use of anti-IgE monoclonal antibodies (omalizumab) in the treatment of DEB-Pr, but currently, no correlation between IgE levels and pathogenicity has been determined [14]. This was also

Table 1: Patient demographics.

Author, year	Country	Study type	Number of patients	Patient sex	Age	Genetic mutation	Comorbid conditions	Prior failed treatments	Level of evidence[†]
Caroppo et al., 2021 [3]	Italy	Case report	1	Female	43	Two heterozygous COL7A1 mutations (c.7344G > A; c.425A > G)	-	Medium-to-high potency topical steroids and systemic antihistamines	4
Clawson et al., 2021 [4]	USA	Case report	1	Male	39	Heterozygous COL7A1 mutation (c.6779G > A)	-	Topical treatments (emollients, clobetasol, bleach water, and pimecrolimus), oral dapsone, and oral cyproheptadine	4
Shehadeh et al., 2020 [5]	Israel	Case report	1	Female	52	Two heterozygous COL7A1 mutations (c.5772A > C; c.6619–2A > T)	-	Potent and super potent topical corticosteroids, topical calcineurin inhibitors, oral fexofenadine, hydroxyzine, promethazine, medicinal cannabis, and St. John's wort	4
Wang et al., 2021 [6]	China	Case report	1	Female	10	Two heterozygous COL7A1 mutations (c.7247G > A; c.946G > A)	-	Systemic and topical corticosteroids and antihistamines	4
Wu et al., 2023 [7]	China	Case series	2[‡]	Patient 1 Male	13	c.6770G > A (p.G2257E); c.2551C > T (p.R851C)	Atopy	Topical and systemic corticosteroids	4
				Patient 2 Female	7	c.8109 + 5_8109 + 11delGTTGAAG	-	Topical and systemic corticosteroids	
Yu et al., 2023 [8]	China	Case report	2	Patient 1 Female	16	Two heterozygous COL7A1 mutations (c. G8234A; c.4128delT)	-	Oral antihistamines, gabapentin, and topical corticosteroids	4
				Patient 2 Male	13	Two heterozygous COL7A1 mutations (c. G8234A; c.4128delT)	-	--	
Zhou et al., 2020 [9]	USA	Case report	2	Patient 1 Male	15	Two heterozygous COL7A1 mutations	Asthma; ADHD	Topical medications (corticosteroids, mupirocin, cannabis, doxepin, KA gel, and OTC antipruritic medications), systemic immunomodulators (corticosteroids, cyclosporine, mycophenolate, thalidomide, lenalidomide, omalizumab, and tofacitinib), systemic antipruritic medications (n-acetylcysteine, gabapentin, pregabalin, naltrexone, melatonin, Marinol, clonidine, antiemetics, antidepressants, and antihistamines), phototherapy, and local destruction of papules	4
				Patient 2 Female	27	Heterozygous COL7A1 mutation	--	Cyclosporine, thalidomide, topical medications (corticosteroids and OTC antipruritic medications), systemic medications (antihistamines, antidepressants, and ondansetron), and phototherapy	

ADHD: attention-deficit/hyperactivity disorder; COL7A1: collagen type VII alpha 1 chain; KA: ketamine-amitriptyline; OTC: over-the-counter; USA: the United States of America. [†]According to the 2011 Oxford Centre for evidence-based medicine, [‡]one patient excluded due to lack of dupilumab treatment. "-" refers to none and "--" refers to not reported.

Table 2: Findings of dupilumab treatment.

Author, year	Dupilumab dose and duration	Pruritus measure	Pruritus findings	QoL measure	QoL findings	EBDASI	Serum IgE level (IU/mL)	Eosinophil level (cells/μL)	Th cell subset (%)	Physical exam post dupilumab	Adverse effects
Caroppo et al., 2021 [3]	Loading dose: 600 mg Maintenance dose: 300 mg Q2W Total duration: 18 months†	VAS	Baseline: 9/10 Week 12: 3/10 Δ: 66.67% decrease	--	--	--	--	--	--	Week 12: significant improvement of erythema and reduction of crusts and scales with flattening of plaques Month 18: great improvement of itching, no new bacterial skin infections	No adverse effects
Clawson et al., 2021 [4]	Loading dose: 600 mg Maintenance dose: 300 mg Q2W Total duration: 9 months†	Descriptive	Baseline: severe Week 2: itching improvement Week 4: nearly complete resolution of pruritus Month 9: symptomatic relief of pruritus continued	--	--	--	--	--	--	Week 4: reduction of new lesions Month 9: slowly resolving skin lesions continued	--
Shehadeh et al., 2020 [5]	Loading dose: 600 mg Maintenance dose: 300 mg Q2W Total duration: 12 weeks†	VAS	Baseline: 9/10 Week 12: 5/10 Δ: 44.44% decrease	DLQI	Baseline: 23/30 Week 12: 8/30 Δ: 65.22% decrease	Baseline: 59/506 Week 12: 51/506 Δ: 13.56% decrease	Baseline: 230 Week 12: -- N/A	Baseline: 600 Week 12: -- N/A	--	Marked improvement in skin exam, with flattening of plaques and significant improvement in redness, scales, crusts, and lichenification over the forearms, elbows, knees, and shins	No adverse effects

Table 2: Continued.

Author, year		Dupilumab dose and duration	Pruritus measure	Pruritus findings	QoL measure	QoL findings	EBDASI	Serum IgE level (IU/mL)	Eosinophil level (cells/μL)	Th cell subset (%)			Physical exam post dupilumab	Adverse effects
Wang et al., 2021 [6]		Loading dose: 600 mg Maintenance dose: 300 mg Q2W Total duration: 7 months†	VAS	Baseline: 5.5/10 Month 7: 1.8/10 Δ: 67.27% decrease	DLQI	Baseline: 13/30 Month 7: 4/30 Δ: 69.23% decrease	--	--	--	--			Day 15: reduced itch and flattening of skin lesions Month 7: significant improvement in skin exam	No adverse effects
Wu et al., 2023 [7]	Patient 1	Loading dose: 600 mg Maintenance dose: 300 mg Q4W Total duration: 20 weeks	VAS	Baseline: 7/10 Week 20: 2/10 Δ: 71.43% decrease	CDLQI	Baseline: 28/30 Week 20: 16/30 Δ: 42.86% decrease	Baseline: 68/506 Week 20: 58/506 Δ: 14.71% decrease	Baseline: 1810 Week 20: 223 Δ: 87.68% decrease	Baseline: 610 Week 20: 340 Δ: 44.26% decrease	Th1 Baseline: 5.65 Week 20: 9.66 Δ: 70.97% increase	Th2 Baseline: 6.86 Week 20: 4.94 Δ: 27.99% decrease	Th17 Baseline: 1.68 Week 20: 5.09 Δ: 202.98% increase	Both showed clinical improvement of symptoms, including partial resolution of nodules and fewer recurrent blisters at week 4; improvement in skin lesions noted over time	No adverse effects
	Patient 2	Loading dose: 600 mg Maintenance dose: 300 mg Q4W Total duration: 20 weeks	VAS	Baseline: 5/10 Week 20: 3/10 Δ: 40.00% decrease	CDLQI	Baseline: 29/30 Week 20: 19/30 Δ: 34.48% decrease	Baseline: 62/506 Week 20: 52/506 Δ: 16.13% decrease	Baseline: 89.6 Week 20: 31.8 Δ: 64.51% decrease	Baseline: 390 Week 20: 170 Δ: 56.41% decrease	Th1 Baseline: 5.27 Week 20: 5.58 Δ: 5.88% increase	Th2 Baseline: 5.34 Week 20: 3.84 Δ: 28.09% decrease	Th17 Baseline: 1.60 Week 20: 4.32 Δ: 170.00% increase		No adverse effects
Yu et al., 2023 [8]	Patient 1	Loading dose: 600 mg Maintenance dose: 300 mg Q2W Total duration: 16 weeks	NRS	Baseline: 6.5/10 Week 16: 1/10 Δ: 84.62% decrease	DLQI	Baseline: 19/30 Week 16: 0/30 Δ: 100.00% decrease	--	Baseline: 386.90 Week 16: -- N/A	--	--			Alleviation of itch and flattening of nodules	No adverse effects
	Patient 2	Loading dose: 600 mg Maintenance dose: 300 mg Q2W Total duration: --	N/A	--	--	--	--	Baseline: normal serum IgE§ Week 16: -- N/A	--	--			Significant clinical improvements	No adverse effects

Table 2: Continued.

Author, year		Dupilumab dose and duration	Pruritus measure	Pruritus findings	QoL measure	QoL findings	EBDASI	Serum IgE level (IU/mL)	Eosinophil level (cells/μL)	Th cell subset (%)	Physical exam post dupilumab	Adverse effects
Zhou et al., 2020 [9]	Patient 1	Loading dose: 600 mg Maintenance dose: 300 mg Q2W Total duration: 22 months	NRS	Baseline: 8/10 Month 18: 4.5/10 Δ: 43.75% decrease	Descriptive	Improved sleep	--	--	--	--	Improved skin findings with flattening and decreased plaques	No adverse effects
	Patient 2	Loading dose: 600 mg Maintenance dose: 300 mg Q2W (until month 6) 300 mg QW (until completion) Total duration: 14 months	NRS	Baseline: 10/10 Month 12: 2/10[‡] Δ: 80.00% decrease	Descriptive	Reduced sleep disruptions	--	--	--	--	Resolution of papular eruption after increasing dupilumab to 300 mg QW	No adverse effects

Δ: change; %: percent; CDLQI: Children's Dermatology Life Quality Index; cells/μL: cells per microliter; DLQI: Dermatology Life Quality Index; IgE: immunoglobulin E; IU: international unit; mg: milligrams; mL: microliters; N/A: not applicable; NRS: numerical rating scale; Q2W: once every 2 weeks; Q4W: once every 4 weeks; QoL: quality of life; QW: once weekly; T cell: T helper cells; Th1: type 1 helper T cells; Th2: type 2 helper T cells; Th17: type 17 helper T cells; VAS: visual analogue scale. [†]Reported long-term treatment with dupilumab anticipated. [‡]After dose adjustment 6 months following loading dose; [§]provided by authors; "-" refers to none and "--" refers to not reported.

represented in our study, as two patients had normal IgE levels but exhibited symptoms of DEB-Pr [5, 7]. Interestingly, dupilumab was still effective in treating their pruritic and cutaneous symptoms [5, 7].

Th2 cytokines, including IL-4 and IL-13, are also involved in inflammation and wound healing, thus enabling the possibility of multimodal symptom alleviation with dupilumab [15]. This was supported in our review in which all subjects reported clinical improvement on physical exam following dupilumab therapy, as well as two studies reporting decreased EBDASI scores [3–9]. Moreover, the increase in C7 reported by Wu et al. highlights a novel clinical benefit in dupilumab therapy, as a reduction in C7 is a hallmark pathological effect seen in this burdensome disease [13]. This raises the possibility of IL-4 and IL-13 playing a fundamental role in the epidermal barrier dysfunction of DEB-Pr [7].

Limitations of our study include a small sample size of subjects due to disease rarity, the paucity of available studies, and the lack of randomized controlled trials regarding dupilumab's efficacy in treating DEB-Pr.

5. Conclusion

Our study supports dupilumab's potential as a treatment modality for patients suffering from refractory itch from DEB-Pr. Furthermore, improved physical exam findings demonstrate dupilumab's ability to treat cutaneous aspects of DEB-Pr including a reduction in inflammation, scaling, and plaques. In addition, one of our studies highlights a novel benefit of dupilumab in which an increase in C7 was shown following treatment. These findings particularly emphasize the importance of Th-2-mediated immunity in the pathological mechanism of DEB-Pr. Before clinical conclusions can be drawn, however, large prospective controlled studies featuring dupilumab treatment for DEB-Pr are needed.

Data Availability

No data were used to support the findings of this study.

Conflicts of Interest

Dr. Peter A. Lio reports research grants/funding from AOBiome, Regeneron/Sanofi Genzyme, and AbbVie; is on the speaker's bureau for Regeneron/Sanofi Genzyme, Pfizer, Incyte, Eli Lilly, LEO, Galderma, and L'Oréal; and reports consulting/advisory boards for Almirall, ASLAN Pharmaceuticals, Bristol-Myers, Dermavant, Regeneron/Sanofi Genzyme, Merck, Pfizer, LEO Pharmaceuticals, AbbVie, Eli Lilly, Micreos (stock options), L'Oréal, Pierre-Fabre, Johnson & Johnson, Unilever, Menlo Therapeutics, Theraplex, IntraDerm, Exeltis, AOBiome, Realm Therapeutics, Altus Labs, Galderma, Verrica, Arbonne, Amyris, Bodewell, Yobee Care, Burt's Bees, My-Or Diagnostics, Sibel Health, and Kimberly-Clark. In addition, Dr. Lio has a patent pending for a Theraplex product with royalties paid and is a board member and Scientific Advisory Committee Member Emeritus of the National Eczema Association. Christopher J. Issa and Aubrey C. Hong have no conflicts of interest.

Authors' Contributions

Christopher J. Issa conceptualized the study, extracted and analyzed the data, and drafted and edited the manuscript. Aubrey C. Hong extracted and analyzed the data and drafted and edited the manuscript. Peter A. Lio reviewed and edited the manuscript.

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