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Review Article

Dupilumab: Newer off-label dermatological indications and clinical implications

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ABSTRACT

Dupilumab, initially approved for atopic dermatitis, has demonstrated promising efficacy in various off-label dermatological conditions. This review explores the growing evidence supporting its use in conditions such as lichen planus, Lichen planus pemphigoids, Kimura's disease, chronic pruritus, and many others. The mechanisms of action, clinical outcomes, and safety profiles associated with dupilumab in these off-label indications are also discussed. As research continues to evolve, dupilumab's potential as a versatile therapeutic option for dermatological disorders becomes increasingly apparent.

Keywords: Dupilumab, Lichen planus, Cutaneous T-cell lymphoma, Kimura disease, Chronic pruritus

INTRODUCTION

Dupilumab has applications for many more dermatological disorders. Part 2 of the review will deal with the utility of dupilumab in lichen planus (LP), Lichen planus pemphigoids (LPP), Kimura's disease (KD), chronic pruritus (CP), chronic actinic dermatitis (CAD), cutaneous T-cell lymphoma (CTCL), 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), hyperimmunoglobulin E syndrome (HIES), hidradenitis suppurativa (HS), neurofibromatosis (NF), recalcitrant palmoplantar pustulosis (PPP), hypereosinophilic syndrome (HES), lamellar ichthyosis (LI), graft versus host disease (GVHD), and trichothiodystrophy (TTD).

LP

Profitability of dupilumab in LP has been expounded in a 52-year-old man who had been unresponsive to systemic corticosteroids (CS) and acitretin. Following 3 months of treatment with dupilumab (label dosing), remarkable improvement in lesions was observed and his numeric rating scale (NRS) itch intensity plummeted from 9/10 to 1/10.[1] In another report, dupilumab (label dosing) promoted rapid resolution of widespread cutaneous LP and generalized pruritus in a 92-year-old female following 2 months of treatment.[2]

The role of Th2 cells and Th2-related chemokines has been proposed in the pathogenesis of LP, with elevated levels of interleukin (IL)-6, which consequently increases IL-4. By inhibiting IL-

4, dupilumab decreases subsequent effector cell function that can have value in LP.[3-5] Nonetheless, more studies are essential to substantiate this concept further.

LPP

LPP is a rare autoimmune immunobullous disorder with overlapping clinical features between LP and bullous pemphigoid (BP). As lichenoid lesions typically precede bulla formation, it is suggested that epitope spreading following lichenoid inflammation and subsequent antibody formation against basement membrane zone proteins are responsible for the lesional phenotype of LPP.[6] Dupilumab decreases inflammation by modulating the signaling of two key cytokines, IL-4 and IL-13 responsible for dysregulating the Th2 cell pathway toward BP180 NC16A (the target autoantibody in LPP), and, in this way, may help in bringing about disease remission.[7]

Literature search revealed two case reports describing the beneficial effects of dupilumab in LPP. In one report (an 18-year-old male), dupilumab (label dosing) monotherapy was employed due to patient concerns regarding treatment with steroids and mycophenolate mofetil (MMF). After 15 weeks of dupilumab treatment, the patient achieved complete clinical remission. Moreover, following 4 months of treatment cessation, the patient remained lesion-free.[7] In the other report (69-year-old man), dupilumab (label dosing) along with prednisolone (50 mg/day) was used for LPP with rapid improvement of lesions in 3 days and 90% clearance by 2 months, along with normalization of the eosinophil percentage and serum anti BP180NC16A immunoglobulin G levels.[8]

KD

KD is a rare, idiopathic benign condition characterized by localized lymphoid proliferation mainly involving the head and neck regions. The Th2 pathway is involved in the pathogenesis of KD, with elevated expression of IL-4, IL-5, and IL-13 messenger ribonucleic acid in peripheral blood mononuclear cells in patients with KD.[9,10] Recent evidence has highlighted the existence of CD4+GATA3+ T-cells in the affected lymph nodes of KD patients, following stimulation by IL-4 and IL-5 synthesize Immunoglobulin E (IgE) with subsequent eosinophil aggregation.[11,12] Inhibition of IL-4 with dupilumab effectively reduces tumor mass by a substantial reduction of eosinophils within the tumour. Besides, this action of dupilumab is independent of IgE. Current literature describing the role of dupilumab in KD is confined to case reports, wherein dupilumab monotherapy, as well as its combination with surgical excision following therapeutic failure with systemic CS, tetracycline, and omalizumab has been employed. In all reports, improvement was demonstrated within a period of 2–16 months, with no recurrence at follow-up. Moreover, dupilumab maintained acceptable levels of safety and tolerability.[13-18]

CP

CP, though a common symptom of dermatologic and systemic medical disorders, can arise even in the absence of a well-defined rash or systemic disease when it is referred to as CP of unknown origin (CPUO). Regardless of its origin, CP markedly impairs the Quality of life of patients and needs to be appropriately managed. Often CP can be refractory to various therapies that include topical/systemic CS, antihistamines, antidepressants, opioid antagonists, cannabinoids, and anticonvulsants.[19]

In CPUO, itch lasts >6 weeks, with recent studies outlining Th2 cytokines such as IL-4, IL-13, and IL-31 being instrumental in promoting pruritus through effects on sensory neurons. By blocking IL-4 and IL-13, dupilumab suppresses neuronal hypersensitivity, thereby alleviating itching.[14] Besides, by decreasing the production of IL-31 from Th2 cells, dupilumab further promotes the improvement of CPUO.[20]

In several reports, the efficacy of dupilumab in CPUO has been demonstrated utilizing numeric scales, including a series of 15 patients wherein the mean itch NRS score reduced by 7 points (standard deviation [SD] 1.9),[21] and a series of six patients outlining a mean reduction of 8.75 points (SD 1.26) for the same.[22] In Zhai *et al.*, case series, the mean NRS itch intensity reduced from 9.6 at baseline to 3.2 at 12 weeks,[23] and in another series, within 4 weeks of dupilumab therapy, highly satisfactory reduction of CPUO was noted, allowing drug withdrawal, with the persistence of the improved status at 20 weeks of follow-up.[24] Interestingly, of all the reported patients, only one had coexistent AD.

Moreover, dupilumab's effectiveness has been outlined in six cases of uremic pruritus (UP).[23,25] Silverberg and Brieva, in their report, elucidated significant improvement of UP in a 45-year-old patient diagnosed with polycystic kidney disease. After 6 months of dupilumab treatment, there was marked improvement in the average pruritus NRS score and Dermatology Life Quality Index (DLQI) by 6 and 11 points, respectively.[25]

Further, in an anecdotal report, dupilumab delineated profitability in the treatment of brachioradial pruritus in a 53-year-old woman with a history of fibromyalgia and bulging cervical disc. Within 3 months of dupilumab therapy, there was 95% improvement of itching.[26] In addition, dupilumab's effectiveness in recalcitrant anal and genital pruritus has been elaborated in an isolated report. Following 1-month of dupilumab therapy, there was a 95% resolution of itching, and physical examination revealed complete

clearance of perianal dermatitis.[27] Interestingly, in a 5-year-old girl with TTC7A mutation, dupilumab (100 mg every 2 weeks) was successful in controlling pruritus as early as a few days following the first injection, with no relapse of pruritus at 1 year of follow-up.[28]

CAD

CAD is an immune-mediated photo-dermatosis characterized by persistent pruritic eczematous plaques involving the sun-exposed sites. Pathogenesis of CAD involves a delayed hypersensitivity reaction to antigens developed in the patient's skin following molecular alteration, secondary to stimulation by ultraviolet (UV) rays. The acute phase of CAD is characterized by Th2 over-activation, whereas in the chronic stage, apart from active Th1 responses, Th2 responses are sustained. Besides, UV irritation suppresses Th1 cells and enhances the antigen presentation capacity of Th2 cells, resulting in a Th1/Th2 disbalance.[29] Further, in CAD, UVB-induced CD3+, CD4+, and CD8- regulatory T-cells mediate their suppressive effects by releasing IL-4 and IL-10.[30] It is suggested that dupilumab particularly interacts with Th2-mediated inflammatory pathways in CAD to bring about disease control.

Five publications have reported the treatment of 11 patients with CAD using dupilumab (label dosing). All patients had failed to appropriately respond to at least one line of previous therapy, such as TCS, methotrexate, MMF, azathioprine, apremilast, hydroxychloroquine, and cyclosporine. Besides, all patients tolerated dupilumab therapy well. Of the 11 patients, conjunctivitis developed in three patients, facial erythema in 1 and diffuse pigmentation in one. However, apart from the patient who developed facial redness, dupilumab therapy continued in others.[31-35]

CTCL

Mycosis fungoides (MF) is the most common variant of CTCL, and Sezary syndrome (SS) is the erythrodermic variant of MF. A predominant Th2 cytokine milieu, similar to AD, consisting of IL-4, IL-5, IL-10, and IL-13 is observed in MF. Besides, MF and SS may often masquerade as adult-onset AD, and SS has been reported in patients with AD during the disease course.[36,37] Theoretically, due to the Th2 cytokine profile, dupilumab may be effective in MF/SS. However, the efficacy of dupilumab in CTCL has demonstrated failure in most reports with exacerbation of existing lesions and development of new lesions,[38-44] Moreover, despite initial improvement with dupilumab, subsequent worsening and disease progression with potentially fatal outcomes of MF/SS has been observed. The initial improvement seen may be following transient blockade of Th2 inflammation, with shifting to a Th1 tumor suppressive effect through interferon-alpha (IFNα) secretion,[36] but as the disease progresses, tumor cells escape dupilumab targeting and resistant clones emerge, making CTCL cells immune to IL-4 and IL-13 blockade.[36,44]

Although few reports have shown dupilumab to be effective in MF/SS, long-term data are lacking, and dupilumab cannot be used as a general drug for MF/SS because there exists no clarity regarding which cases would benefit from dupilumab without worsening. Lazaridou *et al*.,[45] in their series of two patients, highlighted dupilumab to be effective in one patient (55-year-old male), resulting in improvement of pruritus and partial remission of MF after 4 months of follow-up. Mollanazar *et al*.,[46] demonstrated dupilumab to be a highly effective adjunct drug in bringing about dramatic improvement of AD and CTCL in a 68-year-old man where comprehensive multimodality therapy (with bexarotene, IFNα, interferon-gamma (IFNγ), narrow band UVB irradiation, and extracorporeal photopheresis [ECP]) for 6 months resulted only in partial remission. Steck *et al*.,[47] reported marked improvement of skin symptoms after the addition of dupilumab to ECP in a 74-year-old woman with SS.

Nevertheless, as of now given the potential of dupilumab to deteriorate MF/SS, its use in CTCL can only be implemented in selective situations.

WS

WS is an eosinophilic inflammatory disorder whose pathogenesis is poorly understood and is clinically characterized by recurrent cutaneous lesions of variable latency. Overexpression of IL-4/IL-13 is observed in hyper eosinophilic syndromes, which go on to stimulate the recruitment and growth of eosinophils through IgE production and differentiation of B-cells. Further, these activated eosinophils promote release of pre-formed IL-4/IL-13 that potentiate Th2 immune responses.[48]

By directly/indirectly inhibiting eosinophil-associated Th2 inflammatory cascades (through an unknown mechanism), dupilumab may be efficacious in WS. At present, there are two case reports elaborating the benefits of dupilumab in WS.[49,50] In the first report (52-year-old woman), after an initial lesional flare at 4 weeks following dupilumab therapy (label dosing), lesions eventually completely resolved by 6 months.[49] In the second patient (80-year-old woman), dupilumab (400 mg loading dose, and then 200 mg q2w) along with dapsone (100 mg/day) eventuated in almost complete clinical remission within 5 weeks of treatment.[50] Besides, no adverse events were encountered in both reports.

KELOIDS AND HTS

Keloids and HTS represent an increased connective tissue response to meager injury. Both keloids and HTS are benign,

well-demarcated fibrotic growths; only that keloids extend beyond the original margins of the defect, whereas HTS remain confined to the original defect. Elevated expression of IL-4/IL-13 receptors in keloids, as well as increased production of IL-4/IL-13 in chronic lesional and non-lesional keloidal skin provides the basis for dupilumab's implementation in the management of keloids. Furthermore, enhanced levels of IL-13/IL-4 potentiates transforming growth factor-beta signaling in keloidal fibroblasts, and promotes fibrosis through periostin, which again is considerably suppressed by dupilumab.[51,52]

Till date, two reports have elaborated the utility of dupilumab in keloids.[53,54] In the first report (a 53-year-old male with two keloids and concurrent AD), within 7 months of dupilumab therapy, complete disappearance of the smaller keloid and shrinkage of ~50% of the larger keloid was noted, with visibility of normal skin lines.[53] In the second patient (37-year-old woman), though there was no reduction of keloidal size following 3 months of dupilumab treatment, there was near complete absence of her incapacitating symptoms, and she was now able to perform her routine delay activities without any discomfort.[54] Despite the above positive reports, a shared decision-making is essential to employ dupilumab for keloids, due to high costs involved, and optimal duration of treatment still needing elucidation. Besides, non-responsiveness of dupilumab in keloids have also been outlined, making appropriate patient selection critical.[55,56]

For HTS, an isolated report demonstrated dupilumab to considerably alleviate the symptomology and size of lesions after 10 months of therapy. However, as little is known about the cytokine involvement in HTS, more research becomes essential for the same.[57]

GA

GA is a therapeutically challenging necrobiotic disorder. Although Th1 cytokine levels are generally raised in GA, over-expression of the Th2 axis has been recently propounded. By blocking Th2 cytokines, dupilumab may help in the regression of GA in selected patients.[58]

In a recent report of a 74-year-old woman with GA, where potent topical steroids, oral antibiotics, hydroxychloroquine, methotrexate, niacinamide, allopurinol, and adalimumab had failed, dupilumab (label dosing) demonstrated complete clearance of most lesions at 4-week follow-up and significant reduction of erythema and induration in the other lesions, which was maintained at 3 months. Based on this anecdotal report, it needs to be contemplated whether dupilumab can duplicate the efficacious results produced by tumor necrosis factor-alpha (TNFα) blockers in GA, or whether it should be reserved in those GA cases where anti-TNFα therapy has failed.[59]

RPC

RPC is the most common acquired perforating disorder (APD). Although its pathogenesis remains undefined, repeated scratching secondary to intense pruritus constitutes an integral pathogenic trigger for RPC. In APDs, IL-4, IL-13, and IL-31 act as regulators of chronic itch. In addition, IL-4 promotes neuronal hypersensitivity to other strong pruritogens such as histamine, IL-31, and cytokine-thymic stromal lymphopoietin.[60] Due to dupilumab's anti-pruritic properties, the rationale for its use in APDs has been suggested. Besides, when pruritus is reduced, skin trauma eventually decreases, preventing further disease progression.

Ying *et al* recently reported complete clearance of RPC after 3 months of dupilumab in 2 elderly AD patients.[61] This was followed by two individual reports reiterating similar findings. In one report, a nearly complete response was seen after 12 months of dupilumab therapy, whereas in the other, pruritus cleared completely after 2 weeks with gradual amelioration of lesions by 10 weeks of dupilumab therapy.[62,63]

LA

LA is the most common form of primary cutaneous amyloidosis and is often resistant to various forms of therapy. Previous studies elucidate the role of IL-31 for the intense pruritus seen in LA. Besides, IL-13 expression has been detected in keratinocytes and dermal infiltrates of LA lesions.[64,65] By directly blocking IL-13 and IL-4 signaling in sensory neurons, and inhibiting Th2 cells from producing IL-31(a potent itch inciter), dupilumab helps in alleviating pruritus in LA that eventuates in ultimate resolution of skin lesions.[65] The profitability of dupilumab in LA has been elaborated in 2-case reports. Within 2–4 weeks of treatment, dramatic improvement of pruritus was noticed, and by 3 months papular lesions of LA steadily flattened and reduced in size and number.[65,66]

EAE

EAE is a chronic inflammatory disorder presenting as annular erythematous plaques and tissue eosinophilia, and is marked by its refractoriness to most treatments. EAE results following various triggers that lead to IL-5 release, and increased eosinophilic chemotaxis. These activated eosinophils produce IL-4 and IL-13 that facilitate disease persistence. By blocking IL-4/IL-13, dupilumab plummets eosinophil activity, and eventual reduction of eosinophil-related cytokines and IgE.[67] At present, dupilumab's efficacy in EAC has been described in two case reports with favorable results. In both reports, rapid and complete remission of lesions were obtained after the second injection of dupilumab with sustained remission at 5–6 months of follow-up.[67,68]

NS

NS is a rare autosomal recessive genetic disorder characterized by a triad of congenital ichthyosis, trichorrhexis invaginata, and severe atopy. Treatment options for NS are mostly symptomatic and publications regarding the efficacy of biologicals in NS are scarce. Deficiency of lympho-epithelial Kazal-type-related inhibitor (a serine protease inhibitor) in NS impairs the cutaneous barrier, thereby triggering percutaneous allergen sensitization and overproduction of Th2 cytokines.[69] Besides, increased IL-4 production in T-cell subsets induces B-cell proliferation and IgE production.[12] Following antagonism of IL-4Rα by dupilumab, a gradual decline of IL-6/IL-8 is observed (with normal levels of IL-4 and IL-5 remaining). Due to reduced IL-6 levels, B-cell induction and IgE secretion in NS plummets, and decreased IL-8 levels promote reduced dermal neutrophilic chemotaxis, thus alleviating cutaneous inflammation.[70] As of now, dupilumab's utility in NS is confined to case reports/series with improvements visible by 2 weeks to 10 months of therapy. Besides, dupilumab has been well tolerated by patients, with drug discontinuation in two patients being secondary to suboptimal responses, rather than drug-related toxicity.[71-81]

PEO

PEO is a distinct dermatologic entity commonly affecting elderly males and presenting as confluent papules with characteristic sparing of skin folds. Th2 cells are characteristically involved in the pathogenesis of PEO along with elevation in serum thymus and activation-regulated chemokine (TARC) levels. TARC is a Th2-type chemokine that attracts CC chemokine receptor-4-positive cells and is a useful clinical biomarker for PEO.[82] As PEO is a Th2-mediated disease, dupilumab has expressed profitability in its management. In three case reports from Japan, dupilumab (label dosing) was effective in bringing about remission of PEO within 2–4 months of treatment.[83-85] Despite these positive preliminary findings, randomized controlled trials (RCTs) become mandatory to substantiate these results further.

HS

HS is a disorder of the pilosebaceous apparatus commonly involving the intertriginous sites and if extensive, can be debilitating. Expression of enzymes generating sphingomyelins and ceramide are significantly reduced in HS lesional skin, whereas there is an increased expression of enzymes converting ceramide to galactosylceramide and gangliosides.[86] Dupilumab's propitious effects in HS may be linked with its ability to alter the sphingolipid metabolism.[87] Current medical literature elaborates 2 case reports on dupilumab's utility for HS. Both patients (50/43-year-old males) had Hurley stage 2 disease. In one patient following 4 months of dupilumab (label dosing) therapy, Hidradenitis Suppurativa Clinical Response was obtained, whereas in the other patient after 4-months of dupilumab therapy, DLQI reduced to 3 from 25. Besides, both patients tolerated the drug with no adverse events being reported.[87,88]

HIES

HIES is a rare immunodeficiency syndrome presenting as atopic dermatitis, recurrent cutaneous/pulmonary infections, and high serum IgE levels. Clinically and mechanistically, eczema in HIES largely overlaps with AD. Heterozygous mutations in signal transducer and activator (STAT-3) of transcription 3 gene are responsible for the majority of cases of HIES, although other genetic mutations are also encountered. These mutations impair IFNγ production and IL-10 signal transduction, resulting in an unbalanced IL-4 state. Besides, there is a reduction in T-cell receptor signaling along with dysfunction of regulatory T-cells with eventual Th2 cell expansion.[89] Dupilumab's inhibitory effects on IL-4 and IL-13 signaling may explain its efficacy in HIES. Literature search revealed 12 patients with HIES who were treated with dupilumab. Of them, seven had a mutation of STAT-3, three of DOCK8, and one with ZNF391. Pruritus and skin lesions completely resolved in ten patients, and in two patients partial remission was obtained. In all patients, substantial improvement of eczema and pruritus was evident as early as 1–2 months of therapy with dupilumab, along with sustained maintenance as treatment progressed.[90-100]

NF

In an isolated report, dupilumab's effectiveness in reducing the size and swelling of neurofibromas in a patient with type 1 neurofibromatosis (NF-1) who had been primarily started with dupilumab for AD was discovered as a collateral finding. Furthermore, after 16 weeks, besides complete remission of AD, there was no progression of NF-1.[101] The inhibitory effect of dupilumab on neurofibromas may be linked to the interference of IL-4/IL-13 binding to type 1 and type 2 receptors expressed on mast cells and fibroblasts. In this way, excessive production of collagen is halted, thereby inhibiting neurofibroma development.[12] Despite this promising report, the need for more clinical trials has become mandatory to substantiate the utility of dupilumab for this indication.

IMMUNE DYSREGULATION, POLYENDOCRINOPATHY, ENTEROPATHY, AND X-LINKED (IPEX) SYNDROME

IPEX syndrome is an X-linked condition. An anecdotal report of a 2-month-old boy with IPEX syndrome described

dupilumab (200 mg SC every 4 weeks) to be effective in bringing about improvement of pruritus and almost complete resolution of dermatitis following 3-months of therapy without the development of additional autoimmune disorders.[102] Due to FOXP3 mutations in IPEX syndrome, an alteration in the function of regulatory T-cells occurs that skews the immune system toward a Th2 predominance, explaining the propitious effects of dupilumab in this scenario.[102] More clinical reports however are needed to confirm dupilumab's efficacy for IPEX syndrome.

RECALCITRANT PPP

In a report by Smith *et al*.,[103] dupilumab (label dosing) demonstrated efficacy for the treatment of recalcitrant PPP in a 60-year-old smoker woman, who had been unresponsive to various topical agents as well as dapsone, acitretin, apremilast, and secukinumab. Within 30 days of treatment, pustules, pruritus, hyperkeratotic scales, and erythema resolved with residual hyperpigmentation. In PPP, a complex Th2/Th17 cell activation pattern has been identified with a prominent Th2 signature in skin samples and Th-17 skewed inflammation in blood samples. Besides, CD4+ T-cells in the skin and peripheral blood co-express Th17 and Th2 markers, suggesting a Th17-to-Th2 plasticity.[104] Based on these postulations, dupilumab may be beneficial in PPP due to the skewed Th2 pattern.

HES

HES is a rare disorder defined by persistent peripheral eosinophilia (absolute eosinophil count>1.5 × 10^9/L), plus evidence of organ involvement.[105] These disorders are very difficult to treat, requiring immunomodulators that have substantial side effects. With the emergence of biologicals, an alternative treatment modality becomes available in the management of HES.[105,106]

Dupilumab may benefit a subset of patients with HES due to its ability to antagonize IL-4 and IL-13 signaling. A total of 11 patients with HES; seven of which with cutaneous manifestations were treated with dupilumab following failure with systemic steroids. Of the seven patients, five reported varied levels of improvement of skin lesions. In all patients, dupilumab was dosed as per the standard AD schedule, along with other concomitant drugs that included hydroxyurea, gabapentin, and tapering systemic steroids. Improvement of dermatologic lesions was evident by 4–7 weeks of treatment initiation. Besides, all patients tolerated dupilumab, without the occurrence of any major adverse event.[105-107]

LI

LI is a rare autosomal recessive cornification disorder with a variable genetic inheritance pattern. Of late, an association of AD with LI has been iterated. Dupilumab (label dosing) was found to be effective in treating a 22-year-old male with LI and AD, with marked clinical improvement after 3 months of drug initiation.[108] The exact mechanism for the activity of dupilumab in LI still requires elucidation.

GVHD

GVHD is one of the most severe complications of allogenic hematopoietic stem cell transplantation (HSCT) and often presents as a multiorgan disease with cutaneous features being the first to manifest. In two case series consisting of four pediatric patients, dupilumab was successful in treating AD-like GVHD following HSCT, that was recalcitrant to conventional therapies.[109,110] Although the pathogenesis of AD-like GVHD is not clearly delineated, research suggests that it may involve a Th2 response as evidenced by increased levels of eosinophils, IgE, Th2 cells, and regulatory T-cells in some patients,[111] thereby accounting for dupilumab's promising response. Nevertheless, more research is essential to appropriately outline dupilumab's role in GVHD.

FOOD ALLERGY

Dupilumab was effective in allowing a 30-year-old woman with severe AD to tolerate canned corn and pistachios; that had induced anaphylactic shock and generalized urticaria, respectively, earlier on. Dupilumab's effect may be secondary to its inhibitory action on IL-4/IL-13 signaling, reducing the recruitment of MCs at the intestinal level and diminishing the clinical expression of food allergy.[112] However, RCTs need to be undertaken to further substantiate this finding.

TTD

Gruber *et al*.,[113] delineated dupilumab to be effective in an 8-year-old boy with TTD, that was unresponsive to topical glucocorticoids/tacrolimus (0.03%), ceramides and *vitis vinifera* seed oil, as well as systemic antihistamines. Within 3 months of dupilumab treatment, ichthyosis, eczema, and pruritus, all significantly subsided and after 1 year of dupilumab therapy, the patient's skin appeared almost normal. Although the eczema in TTD has not been characterized in detail, it is most likely that a Th2-driven inflammation is responsible, thus making dupilumab helpful here.

ADVERSE EFFECTS

Nasopharyngitis, upper respiratory tract infection, injection site reactions, skin infections, and conjunctivitis are the commonest adverse reactions associated with dupilumab, which is mild-to-moderate in nature.[114,115] Interestingly, trials with dupilumab for asthma and nasal polyposis have

not reported any increased incidence of conjunctivitis; therefore, conjunctivitis may be a risk related to underlying AD pathogenesis and not specifically to dupilumab itself.[114] The safety profile of dupilumab can therefore be adjudged as favorable and consistent, both as monotherapy, as well as in combination with TCS for AD. Nevertheless, long term data is needed to fully determine dupilumab's safety and tolerability.

USE IN PREGNANCY AND LACTATION

Since IgG antibodies can cross the placenta, the possibility of dupilumab's transmission from the mother to fetus exists. In several case reports where dupilumab was discontinued a few weeks after conception, it did not demonstrate any fetal harm. However, more research is mandated to analyze the harmful effects of dupilumab used continually during pregnancy.[116]

It is unknown whether dupilumab is excreted in breast milk or systemic absorption occurs after ingestion. Given the large size of dupilumab, its amount in breast milk is expected to be low. Further, as it gets destroyed in the infant's digestive tract, its absorption is unlikely. Nevertheless, it is crucial to assess the importance of breast milk, along with the mother's medical indication and urgency for dupilumab use.[116]

FUTURE DIRECTION

As dupilumab's propensity to cause immune suppression is considerably low compared to other biologicals, its utility in vesiculobullous disorders as monotherapy, as well as in combination with systemic CS and conventional immunosuppressive drugs needs scrupulous evaluation. RCTs done in this regard can enable outlining a valid protocol regarding dosing schedules and duration of dupilumab therapy for these disorders. Further, due to the risk of infections associated with systemic CS and the usual immunosuppressive agents for vesiculobullous disorders, the therapeutic discourse is often interrupted and does not have a smooth progression. In these situations, dupilumab can prove to be advantageous. However, more evidence is required to confirm these postulations.

CONCLUSION

This review helps to sum up the newer indications of dupilumab in dermatology. Due to its lower propensity in relation to immune suppression, dupilumab can prove to be a valuable alternative in treating a number of dermatoses.

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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