OPEN ACCESS Freely available online

ISSN: 2155-6121
Journal of
Allergy & Therapy

Mini Review

Dupilumab: Breaking Boundaries beyond the Barriers of Atopy

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ABSTRACT

Dupilumab is a monoclonal antibody that blocks the effects of interleukin-4 and interleukin-13 thereby inhibiting Th2-mediated inflammation. It is approved for moderate-to-severe atopic dermatitis requiring systemic treatment. It was expanded to off-label treatment of numerous dermatological conditions. We provide an update on the increasing scope of uses of dupilumab in rare and common dermatological diseases refractory to frontline therapy. PubMed/MEDLINE database were searched for articles mentioning the term 'dupilumab', excluding the terms “atopic dermatitis”, “asthma” and “nasal polyps”, then manually reviewed to identify published data on the off-label dermatologic uses of dupilumab that were not mentioned in previous reviews. Dupilumab appears to be an effective treatment for several dermatologic conditions including congenital ichthyosis, dermatitis related to immunodeficiency disorders, non-immune bullous diseases and acantholytic disorders. In the context of atopic dermatitis, it seems to reduce associated bacterial and viral infections. Dupilumab was successfully used as an off-label treatment in many recalcitrant skin diseases. However, more studies are required to support the preliminary evidence provided by case reports and case series.

Keywords: Dupilumab; Atopic dermatitis; Asthma; Nasal polyps

INTRODUCTION

Dupilumab has been under the spotlight as the first biologic agent used to treat patients with Atopic Dermatitis (AD). It is a fully human monoclonal IgG4 antibody that blocks the shared alpha subunit of the interleukin (IL)-4 and IL-13 receptors. The significant improvement of AD symptoms has been investigated in several placebo-controlled phase 2 or 3 randomized clinical trials that recruited patients with moderate-to-severe AD resistant to standard therapy [1-6].

The European commission gave its approval for moderate-to-severe AD in patients aged 6 years and above. Lately, the literature has seen a rapid rise in case reports that have demonstrated the use of dupilumab as an emerging off label treatment option for other skin diseases. The literature review by Muñoz et al. has described this off-label use in common and rare cutaneous diseases including prurigo nodularis, eczema (nummular, allergic contact or hand eczema), chronic urticaria, autoimmune bullous disease and alopecia areata [7]. Since then, numerous additional skin conditions treated by dupilumab have been reported, including the paper by Barranca et al. in this issue of the journal of allergy and therapy that describes the clinical and biological effects of dupilumab in peeling skin syndrome, a very rare form of congenital ichthyosis. This justifies an update of the latest and novel off-label uses of dupilumab in skin diseases.

GENETIC DISEASES

Congenital ichthyoses

Dupilumab has been used in Netherton Syndrome (NS), a syndromic form of ichthyosis with autosomal recessive inheritance, due to SPINK5 mutation and characterized by the triad alopecia (trichorrexis invaginata), inflammatory skin lesions and atopic features. The previous review by Munoz et al. has already reported the cutaneous effects of dupilumab in 4 patients with NS [8-11]. Since then, new case reports have evaluated the effect on hair

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Received: 16-Apr-2022, Manuscript No. JAT-22-16133; **Editor assigned:** 18-Apr-2022, Pre QC No. JAT-22-16133 (PQ); **Reviewed:** 04-May-2022, QC No. JAT-22-16133; **Revised:** 12-May-2022, Manuscript No. JAT-22-16133 (R); **Published:**19-May-2022, DOI: 10.35248/2155-6121.22.13.286

Citation: Altandi SA, Freire MS, Hautier JM (2022) Dupilumab: Breaking Boundaries beyond the Barriers of Atopy. J Allergy Ther. 13:286.

anomalies [12-14]. Trichoscopic analysis of 3 NS revealed an increase in average hair length and smoothness that paralleled the improvement of skin lesions and the reduction of scalp itching [12,13]. One of the 3 patients had a resolution of trichorrexis invaginata [13].

In peeling skin syndrome, a very rare form of congenital ichthyosis, dupilumab did not significantly improve skin syndrome and symptoms despite a significant reduction of IgE levels [15].

Dupilumab was also used in a patient with trichothiodystrophy, another autosomal recessive syndromic ichthyosis characterized by several associated anomalies including brittle hair, intellectual impairment, short stature and ocular abnormalities [16]. For this patient, dupilumab led to near-total resolution of scaling, erythema and itching, as well as improved hair thickness during 1 year of therapy.

Immunodeficiency associated dermatitis

Tetratricopeptide repeat domain 7A (TTC7A) deficiency is an autosomal recessive disorder characterized by intestinal atresia, severe combined immunodeficiency and skin anomalies including ichthyosis, pruritus, alopecia and nail hyperkeratosis. Dupilumab was effective in improving skin lesions and intense refractory pruritis in a 5-year-old girl [17-19].

In two cases of DOCK8-deficiency dermatitis (an autosomal recessive combined B and T cell immunodeficiency characterized by eczematous lesions, respiratory and skin infections, elevated IgE and severe atopy), dupilumab was used as a temporizing treatment before hematopoietic stem cell transplantation, and induced a reduction of pruritus, skin lesions and infections) [20]. Likewise, improvement of skin anomalies were seen in 2 patients with severe dermatitis secondary to hyper IgE syndromes due to STAT 3 mutations [21,22], one patient with IgG4 associated dermatitis [23] and one patient with severe generalized eczema in the context of common variable immunodeficiency [24].

Epidermolysis Bullosa Pruriginosa (EBP)

EBP is a rare form of epidermolysis bullosa due to autosomal dominant or recessive mutations in COL7A125 and is characterized by bullae and erosions in the neonatal period, followed by lichenified papules, scarring and intense pruritus in adolescence or early adulthood. A recent retrospective study examining the biological profile of EBP patients revealed elevated IgE levels and increased Th2 subsets on immunophenotyping, suggesting a role of Th2 inflammation in the disease [25,26]. A total of 6 patients with EBP experienced a remarkable reduction in itch, rapid healing and a decrease in number of new lesions [27-31]. One patient experienced an "end-of-dose" effect with a relapse of pruritus prior to successive injections that was successfully managed by increasing the frequency of the injections. 28 Results were maintained throughout treatment and sustained from 3 to 22 months.

ACANTHOLYTIC DISORDERS

Hailey-Hailey disease

Is an autosomal dominant blistering dermatosis due to ATP2C1 mutations? The literature review revealed 3 cases of treatment-resistant Hailey-Hailey disease responding to dupilumab [32]. These 3 patients experienced a remarkable improvement of skin lesions after 2 months. This response was sustained throughout the course of therapy and in one case treatment interruption led to a transient relapse that eventually subsided after restarting therapy.

Grover's disease

Presents clinically as a pruritic, erythematous papulovesicular eruption affecting the trunk and extremities in males around the sixth decade of life.

The coexistence of Grover's disease with other cutaneous diseases including AD, contact dermatitis and xerosis [33] has led some authors to hypothesize the involvement of Th2 inflammation. There are 5 cases of recalcitrant Grover's disease reported in the literature for which dupilumab was used [34-36], including a severe case secondary to immunotherapy with ipilumab/nivolumab for treatment of metastatic renal cell carcinoma [33]. In all patients, dupilumab led to a significant amelioration in pruritus as early as 2 weeks after treatment and a total resolution of skin lesions.

EOSINOPHILIC DERMATOSES

Eosinophilic Dermatoses of Hematological Malignancy (EDHM, previously named insect-bite like reaction) is a chronic pruritic polymorphic eruption without effective treatment, occurring in association with haematological malignancies, notably chronic lymphocytic leukemia [37]. Four cases treated by dupilumab achieved a rapid resolution of pruritus and nearly complete clearing of the eruption after the first few injections, and lasting 4 to 6 months [38-40].

Well's Syndrome (WS) is an eosinophilic hypersensitivity reaction characterized by rapid-onset oedematous and pruritic urticarial plaques that may occur in association with underlying inflammatory diseases, infections, medications and/or malignancy. One patient with asthma, nasal polyps and long-standing disease had a marked improvement after 6 months of dupilumab [41].

Kimura's Disease (KD) is a chronic relapsing inflammatory disease most commonly affecting middle-aged Asian males and presenting with subcutaneous masses located on head on neck areas and composed of follicular hyperplasia with eosinophilic infiltrates [42]. Th2 inflammation underlies the pathogenesis of the disease and leads to hypereosinophilia, elevated immunoglobulins E, IL-4 and IL-5. Systemic corticosteroids are the main stay of therapy, other therapies including surgery and radiotherapy. Dupilumab was successful as a post-surgical adjuvant treatment in one patient with continued remission after 1 year on therapy [43]. In another patient, dupilumab alone achieved complete remission of a 10-year subcutaneous nodule [44].

OTHER DISEASES

A patient with lichen planus recalcitrant to topical and oral corticosteroids as well as acitretin, had a dramatic response to dupilumab with significant reduction of skin lesions and pruritus, maintained for at least 2 months [45].

Lichen amyloidosis is characterized by extracellular deposition of an amyloid protein in skin leading to pruritic hyperkeratotic grayish-brown coalescing papules. Dupilumab was effective in treating 2 patients with widespread lesions, one with concomitant AD [46,47]. Within 2 to 4 weeks, there was complete resolution of pruritus as well as a reduction of skin lesions that was maintained during 9-months [47].

In granuloma annulare, Min et al. found highly upregulated levels of IL-4 in skin lesions, compared to normal skin, providing a rationale for the use of dupilumab [48]. In one patient, with generalized, recalcitrant disease, dupilumab was found to clear most of the lesions [49].

CUTANEOUS INFECTIONS IN THE CONTEXT OF AD

Dupilumab was reported as an effective drug for reducing cutaneous infections in the context of AD. A pooled analysis of AD patients found that the use of systemic antibiotics was remarkably decreased under dupilumab [50]. Regarding viral infections, dupilumab use was associated with less frequent herpes infections [50]. This could be attributed to reduced scratching, improvement in skin barrier, reversal of antimicrobial peptide reduction, reduction of steroid and immunosuppressive medication use. In one patient with AD on dupilumab, there was also a reduction of genital condylomas [51]. With regards to molluscum contagiosum, a total of 7 patients experienced complete resolution of their lesions with dupilumab [52-55]. (one of whom had transient dissemination before complete regression) [55,56], while one patient had a rapid dissemination of pre-existing lesions after 8 weeks on dupilumab, motivating an interruption of treatment [57,58].

CONCLUSION

IL-4 and IL-13 blockade by dupilumab could be a safe and effective treatment for many cutaneous diseases, as reported in the review by Muñoz et al. Other diseases with IL-4 and IL-13 mediated type 2 inflammation, such as systemic sclerosis and scleromyxoedema, are other possible future candidates for dupilumab.

It is important to keep in mind that at present, it remains an off-label, expensive and second line treatment for all these diseases. Additional studies (ideally randomized controlled trials) will be necessary to conclude and define the exact place for dupilumab in the therapeutic armamentarium.

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