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REVIEW



Dupilumab in real-life settings: a review of adverse events and their pathogenesis

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ABSTRACT

Introduction: Dupilumab is a safe and effective biological drug that revolutionized the treatment of atopic dermatitis (AD). Concerning adverse events (AEs), the most commonly reported included ocular involvement, nasopharyngitis, and injection site reactions in clinical trials. Anyway, its use in daily practice is revealing novel dupilumab-induced manifestations.

Areas covered: Relevant English literature (real-life studies, case series, reviews, and meta-analyses) regarding real-life adverse events induced by dupilumab were searched for up to 10 June 2023.

Expert opinion: Dupilumab is an effective treatment for AD, showing favorable safety profile since no routine laboratory monitoring is recommended. However, several cutaneous and extracutaneous AEs have been reported in real-life setting expanding the pool emerged from clinical trials. In detail, dupilumab may determine de-novo onset or exacerbation of preexisting conditions, whose pathogenesis is still unclear and seems to involve Th1/Th2 and Th2/Th17 immune-response imbalance. Also, the heterogeneity and the variable onset time of AEs with respect to dupilumab initiation warrant a thorough patients' history collection and strict short- and long-term monitoring. Finally, the most appropriate management of patients with AEs related to dupilumab should take into consideration efficacy for AD as well as severity and nature of the AE, available treatment and patients' preferences.

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KEYWORDS

Adverse event; dupilumab; pathogenesis; real-life; safety

1. Introduction

Dupilumab is a human monoclonal antibody targeting the alpha subunit of the interleukin (IL)-4-Receptor (IL-4 R α), inhibiting both the IL-13 and IL-4 pathways. It is currently approved for the treatment of moderate-to-severe atopic dermatitis (AD) of the adults and severe atopic dermatitis of children above the age of 6 months [1]. Although striking efficacy and safety outcomes in the treatment of AD, many adverse reactions have been described, including ocular involvement (conjunctivitis and keratitis), nasopharyngitis and injection site reactions, being reported as the most common ones [2]. Interestingly, the increasing and widespread use of dupilumab in clinical practice has led to the emergence of novel adverse events (AEs) as justified by the greater heterogeneity of patients with respect to clinical trials' populations. Among them, alopecia areata, psoriasis, arthritis, lymphoma, red face, skin peeling, rosacea-like eruptions, vitiligo, and morphea have been reported. To collect the adverse events related to dupilumab emerged in real-life settings, we performed a review on the available literature data.

2. Methods

A literature search was performed using PubMed, Embase, The Cochrane Library, and Google Scholar databases up to 10 June 2023. The included keywords were 'dupilumab,' 'adverse event,' 'adverse reaction,' 'real-life,' 'alopecia areata,' 'psoriasis,' 'vitiligo,' 'morphea,' 'skin peeling,' 'red face,' 'paradoxical erythema of the head and neck,' 'rosacea,' 'lymphoma,' and 'arthritis.' All real-

life studies, case series, as well as meta-analysis and reviews were included. References were reviewed in order to include studies that may have been missed and remove those already discussed in the review in order to avoid duplicates. A summary of the included articles is shown in Table 1.

3. Results

3.1. Alopecia Areata

Alopecia areata (AA) is an immune-mediated non-cicatricial hair loss disorder affecting about 2% of the general population [3]. Clinically, it may present with patches of hair loss on the scalp or head (patchy AA), involve the whole scalp (AA totalis) and the entire body hair (AA universalis). On a molecular level, AA is provoked by the hair follicle immune privilege collapse with the local increase in the level of interferon-gamma (IFN- γ) and CD8+ T cells, suggesting the key role of the Th1/Th17 immune response in its pathogenesis.

During dupilumab treatment, cases of new onset, reactivation or exacerbation of AA have been observed.

Napolitano et al. recently reported the results of a retrospective study on the adverse events related to dupilumab therapy in a cohort of 916 patients with AD. They described the onset of AA, clinically diagnosed, in 11 out of 916 (1.2%) patients after 8.23 ± 4.56 months from treatment start, for which topical corticosteroids ($n = 9$, 81.82%) and minoxidil ($n = 2$, 18.18%) were prescribed successfully without dupilumab withdrawal. Complete hair

Article highlights

- Dupilumab is a biological agent targeting the alpha subunit of the interleukin (IL)-4 receptor, thus inhibiting IL-4 and IL-13 pathways;
- The safety profile of dupilumab is favorable with ocular manifestations, nasopharyngitis and injection site reactions as the most common adverse events (AEs) in clinical trials;
- Real-life settings, where dupilumab is increasingly used, have depicted a wider spectrum of AEs, including cutaneous, articular, and neoplastic findings.

regrowth was observed after 3.56 ± 2.48 months from treatment start [4].

Sachdeva et al. conducted a systematic review on the occurrence of AA during treatment with dupilumab for AD collecting all the available data up to June 2020. They reported 17 cases of new onset ($n = 14/17$, 82.4%), reactivation ($n = 2/17$, 11.8%), or exacerbation ($n = 1/17$, 5.9%) of AA that occurred with a mean latency time of 17.6 weeks from treatment start in predominantly male patients ($n = 12/17$, 70.6%) with a mean age of 34.1 years. Interestingly, AA partially (PR) or completely (CR) resolved in 13 out of 17 patients ($n = 6$, $n = 7$, respectively) within 14 weeks. Of them, five patients with CR and two with PR stopped dupilumab and most of them received specific AA therapies. The authors postulated that the Th2 inhibition determined an amplification of Th1/Th17 pathway pathogenetically involved in AA. Interestingly, the same authors collected data about 11 patients, mainly males ($n = 6$, 54.5%) with a mean age of 35.0 years, with AA that improved after a mean time of 2.3 month from dupilumab start. All patients experienced hair regrowth that was partial in 63.6% ($n = 7$) and complete in 36.4% ($n = 4$) with a mean resolution time of 6.3 and 15 weeks, respectively. It has been supposed that the IL-4 signaling pathway inhibition may result in the reduction of IL-4 depending inflammatory mediators such as IgE, mast cells, and eosinophils leading to betterment of AD as well as AA [5].

Afterward, other few cases of AA during dupilumab have been reported.

Kulkarni et al. described the case of a 22-year-old African American male patient with severe AD that experienced the occurrence of patchy AA of the scalp 10–12 weeks after dupilumab start. For this reason, the biologic therapy was initially withdrawn and immunomodulant treatment (with mycophenolate mofetil and intralesional and topical corticosteroids) undertaken and then started again at a low dose with complete hair regrowth [6].

Yamane and colleagues described the occurrence of de novo AA in a 31-year-old Japanese man under dupilumab three months from treatment start with hair regrowth with proper topical corticosteroids after 2 months [7].

Overall, AA appears to occur between 2 days and 28 months from dupilumab initiation, regardless of a previous history of AA, with hair regrowth between 3 weeks and 6 months from drug withdrawal if needed, or in response to topical corticosteroid treatments [8]. It seems that most of patients are young males with AD as the solely comorbidity [9].

There are several hypotheses concerning the development of AA under dupilumab: first, the Th1/Th17 polarization induced increases the level of INF inside the hair follicle provoking the

immune privilege collapse; second, the inhibition of IL-4 and IL-13 that are involved in the expression of sebaceous gland signature results in their atrophy, picture typical of drug-induced AA. Whether this entity is a pure AA or AA-like reaction is still debated, and more research on the IL-17 and IL-23 pathway must be carried out. Moreover, further investigation is warranted on the topic since there are trials and case reports reporting improvement of AA during dupilumab treatment [5]. Apparently, the female sex and the presence of AD and other atopic comorbidities such as asthma and food allergies may play a role in such phenomenon [9]. It has been postulated that the presence of a strong Th2 polarized immunity may cause the reduction in Treg cells and the production of IL-13. In parallel, Tregs seems to be necessary to the proliferation and differentiation of the hair follicle in the anagen phase and are decreased in AA. Hence, the Th2 inhibition leads to the restoration of Tregs with hair regrowth [9]. In support of such hypothesis, Renert-Yuval and colleagues demonstrated a robust correlation between SALT improvement and changes in scalp Th2- and Th1- biomarkers (IL-10, CCL18/PARC, CCL13/MCP-4, and IFN γ and CXCL9) in patients with AA treated with dupilumab, highlighting the role of Th1/IFN gamma in promoting AA phenotype, introducing the idea that early Th2 tackling may allow follicular immune privilege restoration [10].

3.2. Psoriasis

The occurrence of psoriasis as adverse event during dupilumab therapy is being frequently reported in real-life settings. Interestingly, pathogenetically, the dupilumab-induced polarization of immune response toward Th1 may make Th1-driven diseases, such as psoriasis, evident, although molecular studies that address the topic must be carried out [11]. Indeed, it has been shown that AD presents as a polar Th2 disease in the acute phase, with a partial shift to Th1 during the chronic phase. On a molecular level, IL-4 is a negative regulator of Th1 and Th17 cells, that can modulate the phenotype of dendritic cells resulting in a suppression of IL-23 production. As a result, the selective inhibition of IL-4 produced by dupilumab may determine the induction and maintenance of pathogenic Th17 cells, predominant in psoriasis, leading to the appearance of psoriatic manifestations [12].

A recent review by Su et al. collected the cases of dupilumab-associated psoriasis (DAPs) and psoriasiform manifestations (PsM). 31 articles reported 47 affected patients (including 37 adults and 10 children), of whom 44 presented with de novo psoriasis and 3 patients with flares of preexisting psoriasis during dupilumab treatment. Concerning the adult population, the mean time of de novo onset of psoriasis from dupilumab start was 4.3 months (1–18 months); by contrast, in children it was 6.4 months (2–12 months). Interestingly, the dupilumab-associated flares of psoriasis occurred slightly earlier, at about 3.3 months from treatment start. Few cases showed a long onset time ranging from 1.5 years up to 2.5 years [13]. Thus, the authors recommend to screen for psoriasis manifestations within the first year of treatment, notwithstanding the need for a long-term follow up given the scarcity of data on the topic [13].

Table 1. Summary of the included studies.

Authors	Type of study	N. of patients	Pre-existing condition	Mean onset time from dupilumab start	Resolution
Alopecia Areata					
Sachdeva et al. [5] 2021	Systematic review	17-De novo ($n = 14/17$, 82.4%), -Reactivation ($n = 2/17$, 11.8%), -Exacerbation ($n = 1/17$, 5.9%)	Yes/No	17.6 weeks	-PR $n = 6/17$ -CR $n = 7/17$ within 14 weeks.
Kulkarni et al. [6] 2022	Case report	De novo 1	UNK	10–12 weeks	Yes, almost CR at 15 months from baseline and 3 months from Dupilumab low dose started
Yamane et al. [7] 2022	Case report	De novo 1	No	3 months	Yes, 2 months after topical CCS without dupilumab interruption
Napolitano et al. [4] 2023	Retrospective study	De novo 11/916	UNK	8.23 ± 4.56 months	Yes, 3.56 ± 2.48 months after topical TCs and minoxidil start without dupilumab interruption
Psoriasis					
Su et al. [13] 2023	Review	47 patients (37 adults, 10 children) 44 de novo 3 preexisting psoriasis	Yes 3 cases	De novo psoriasis Adults: 4.3 months Children: 6.4 months Pre-existing psoriasis flares: 3.3 months	Yes, some patients discontinued dupilumab
AA and psoriasis					
Maolini et al. [14] 2021	Case report	1 De novo AA-like psoriasis +	No	5 months	Yes 9 months after topical CCS + calcipotriol start
Beaziz et al. [15]	Case report + Review	Body psoriasis 1	No	1 year	Yes, 2 months after topical CCS.
Vitiligo					
Takeoka et al. [17] 2021	Case report	1	Yes	3 months	No, only small repigmentation 17 months after treatment withdrawal
Napolitano et al. [4] 2023	Retrospective study	2/916	1: yes 1: no 4: no 3: yes	1.97 ± 2.67 months	Yes, after 4.31 ± 2.67 months from TCs and nb-UVB phototherapy, without dupilumab discontinuation
Ren et al. [18] 2023	Multicenter report	7		3.4 ± 1.6 months	Yes in 6/7 cases without dupilumab withdrawal. No, in one case notwithstanding treatment discontinuation
Lymphoma					
Park et al. [19] 2022	Review	27	Yes/No	23: AD 3: MF 1: psoriasisform dermatitis Were all diagnosed with MF at different stages after a mean of 7.8 months from treatment start	N/A MF/SS
Arthritis					
Hughes et al. [27] 2023	Observational study	26/470	UNK	UNK	Yes, in 22 patients, 7 of which interrupted dupilumab No, in 4 patients notwithstanding dupilumab interruption
Raimondo et al. [28] 2022	Case report	1	No	26 months	Yes, symptom improved under baricitinib treatment
Jay et al. [26] 2022	Review + case series	38 + 3	No	Within 4 months	Depending on the severity of joint symptoms and efficacy of adjunctive anti-inflammatory drugs

(Continued)

Table 1. (Continued).

Authors	Type of study	N. of patients	Pre-existing condition	Mean onset time from dupilumab start	Resolution
Skin peeling					
Napolitano et al [4] 2023	Review	11	No	After the first loading dose of dupilumab	Yes, complete spontaneous resolution within 7 days without dupilumab discontinuation
Hammadi et al [29] 2019	Case Report	3	No	After the first loading dose of dupilumab	Yes, complete spontaneous resolution within 2 weeks without dupilumab discontinuation
Red face					
Jo et al [31] 2021	Review	101	No	4–39 weeks	29 patients experienced improvements, while 4 demonstrated complete clearance. By contrast, 16 patients did not show any improvement, 8 worsened and 11 of them discontinued dupilumab for the scarce control of the red face notwithstanding specific treatment
Russo et al [32] 2022	Case series	6	No	8–20 weeks	Spontaneous resolution was observed with no treatment discontinuation.
Morphea					
Kassamali et al [35] 2021	Case report	1	No	8 months	Yes, dupilumab was discontinued and mycophenolate mofetil started with improvements in 7 months
Wang et al [34] 2022	Case series	2 pediatric patients (1 female, 1 male)	No	1 female: 34 months 1 male: 5 months	Dupilumab was discontinued in both cases. Female: Improvement of morphea after methotrexate and corticosteroids within 6 weeks. Male: Worsening of morphea notwithstanding topical and systemic corticosteroids, methotrexate and mycophenolate mofetil.
Rosacea-like eruption					
Quint et al [36] 2020	Review	6	No	3–36 weeks	UNK
Falcinelli et al [37] 2023	Case report	1	No	3 years	Dupilumab was discontinued and rosacea improved and relapsed once the biological agent was restarted

PR, partial resolution; CR, complete resolution; UNK, unknown; nb-UVB, narrow-band ultraviolet B; TCs, topical corticosteroids; CCS, corticosteroids; MF, mycosis fungoides; SS, Sezary Syndrome.

Concerning the pathogenesis, it has been shown that DAPs have the same low prevalence of that of classical psoriasis and concomitant AD and psoriasis suggesting that the occurrence of psoriasiform manifestations may be driven by the administration of dupilumab as extrinsic trigger.

Overall, in the setting of psoriasis and psoriasiform manifestations induced by dupilumab, it is important to provide effective treatment for AD and at the same time to control the severity of these manifestations. Indeed, for severe forms of DAPs/PsM, dupilumab discontinuation is recommended and drug reintroduction discouraged due to the high risk of psoriasis recurrence. In the study, 48.5% of patients that discontinued dupilumab achieved remission with the aim of topical or systemic treatments [13].

3.3. AA and psoriasis

Interestingly, more than one AE may occur concomitantly while on dupilumab treatment.

Maiolini et al. reported the case of AA-like psoriasis of the scalp and psoriasis of the body in a 22-year-old male patient 5 months after dupilumab initiation for severe AD. Treatment with topical calcipotriol and betamethasone dipropionate was started and hair regrowth was observed 9 months after [14].

Beaziz et al. reported the occurrence of AA and psoriasis in the context of dupilumab for the treatment of AD in a 45-year-old man. The patient developed the diseases after 1 year from treatment start that resolved with the addition of topical clobetasol propionate 0.05% 2 and 6 months after [15].

3.4. Vitiligo

Vitiligo is an immune-mediated cutaneous disease characterized by the selective destruction of melanocytes by cytotoxic CD8+ T cells. These cells are responsible for the production of inflammatory cytokines such as IFN γ and tumor necrosis factor (TNF) that create an inflammatory environment through a positive feedback mechanism [16].

There are only few reports on the development or worsening of vitiligo under dupilumab.

Takeoka et al. described a 17-year-old patient affected by severe AD and vitiligo vulgaris that started dupilumab with two opposite outcomes, improvement of the first and worsening of the second as early as 3 months with no recovery after 17 months from treatment withdrawal. Probably the Th1/Tc1 polarization induced by dupilumab had determined the production of IFN and TNF alpha with worsening of the preexisting vitiligo [17].

In the retrospective study by Napolitano et al., vitiligo was reported in 0.21% ($n=2/916$) of patients under dupilumab for AD after 1.97 ± 2.67 months. A man and a woman with a mean age of 52 ± 38.18 years, that experienced vitiligo resolution with topical corticosteroids and narrow-band Ultraviolet B (nb-UVB) phototherapy after 4.31 ± 2.67 months, without discontinuing the biological agent [4].

Finally, Ren et al. presented a multicenter report of seven patients with induced or exacerbated vitiligo after a mean of 3.4 ± 1.6 months from dupilumab initiation for severe AD ($n=$

5, 71.0%) or nasal polyposis ($n=2$, 28.6%). Of seven patients, four reported a new onset vitiligo, while three subjects had a stable form that worsened during therapy with the biological agent. Prescribed treatments included topical corticosteroids, calcineurin inhibitors, and jak-inhibitors with/without nb-UVB phototherapy with control of the disease in 85.7% of cases. Only one patient discontinued dupilumab with no improvement of vitiligo [18].

3.5. Cutaneous T cell lymphoma (CTCL)

CTCL represents a heterogeneous group of diseases characterized by the monoclonal proliferation of T lymphocytes in the skin, appendages and mucosae. According to the WHO-EORTC Classification 2018, CTCLs constitute about 75% to 80% of all primary cutaneous lymphomas in Western countries, with mycosis fungoides (MF) as the most common phenotype.

A growing number of studies have reported the unmasking or progression of cutaneous T cell lymphomas after dupilumab therapy. In detail, dupilumab by competitively inhibiting the IL-4 and IL-13 binding to the IL-4 α 1 subunit receptor, prevents tyrosine kinase downstream pathway activation and related Th2 inflammation. It seems that the increase in free IL-13 levels determines the massive binding to IL-13 α 2 subunit receptor (IL-13 α 2) which has been shown involved in cell proliferation, invasion and immune evasion of several cancers including cutaneous lymphomas. Anyway, whether this phenomenon is related to a pre-treatment misdiagnosis (i.e. atopic dermatitis-like primitive cutaneous lymphomas) or a direct effect of dupilumab is yet to be clarified.

Park et al. in 2022 conducted a review on the cases of CL following treatment with dupilumab. Twelve studies (nine case studies, one case series, one case review, and one cross-sectional retrospective cohort study) including 27 patients were collected and analyzed. Patients were mainly males ($n=15$, 55.5%) with a mean age of 57 years (range 27–77). At dupilumab start, 23 out of 27 were presumably diagnosed with AD, 3 with MF, and 1 with psoriasiform dermatitis. Afterward, all of them but 3 (CTCL-not otherwise specified, CTCL-NOS) were diagnosed with MF, and those with the MF initial diagnosis experienced a dramatic worsening of their condition till stage IVa. The authors encourage to take several biopsies before and during treatment with dupilumab, especially for non-responder patients and regardless of T-cell receptor (TCR) gene rearrangement since it may be equivocal or negative, and to stop the therapy at the diagnosis of CL [19].

Other than classic MF/Sézary Syndrome (SS), CD8+ MF, angioimmunoblastic T-cell lymphoma, and CD30-positive anaplastic large-cell lymphomas have been described under dupilumab [20–23].

Jfri et al. ran a recent review on the MF and SS developed after dupilumab treatment for presumed AD. They identified 23 cases from 11 studies, with mean age of 58 years (range 27–74) and mainly adult-onset AD ($n=19$, 82.6%). Interestingly, of these only five had clinical and histological presentations consistent with AD pre-dupilumab, suggesting that the drug can promote MF/SS development or unmask subclinical forms as their diagnosis may be subtle [24].

3.6. Arthritis

The first report of dupilumab-associated inflammatory arthritis was described in 2019 in 3 patients within 4 months from treatment start. The reported estimated prevalence is about 5%, that may be overestimated due to the scarcity of data on the topic. Concerning pathogenesis, the blockade of IL-4 α receptor induced by dupilumab reduces the protective effect of the IL-4/IL-13 axis on the IL-23/17 one, with consequent arthritis elicitation in predisposed patients. Future interesting studies would be focused on the role of IL-13 in the process, through the experience with selective anti-IL13 molecules [25].

Jay et al. conducted a review on the occurrence of arthritis during treatment with dupilumab. They found out that the onset of the process usually starts within 4 months from dupilumab initiation, ranging from immediately after the first injection to several months. Moreover, arthritis appears to resolve with dupilumab withdrawal. Most of the patients reported a generalized involvement, others oligoarticular or focal forms, and the severity was mainly mild to moderate. The authors propose some recommendations to screen for and manage the occurrence of the side effect, considering anti-inflammatory agents as an add-on therapy in case of mild-to-moderate forms without discontinuing the drug, if possible, leaving it to the most severe cases [26].

Hughes et al. described the onset of musculoskeletal (MSK) syndrome of inflammatory enthesitis, arthritis, tenosynovitis in 26 patients of 470 under dupilumab for AD. The severity was mild in 16 cases, moderate in 6 and severe in 4. Treatment prescribed included nonsteroidal anti-inflammatory drugs (NSAIDs). Overall, 15 subjects continued dupilumab with MSK symptom resolution, while 11 discontinued. Of those, 7 had MSK symptom disappearance, while 4 persisted [27].

Raimondo et al. reported the case of a 44-year-old man with severe AD that developed an acute seronegative axial spondylarthritis after 26 months from dupilumab start. Notwithstanding the great cutaneous benefit, the biological agent was withdrawn and replaced first by an anti-IL17 one (secukinumab), then by a Janus Kinase (Jak)-inhibitor (baricitinib) for primary inefficacy [28].

3.7. Skin peeling

Skin peeling, defined as a fine cutaneous desquamation, has been reported as novel adverse events in real-life studies concerning the use of dupilumab. Indeed, there are increasing case series shedding light on such interesting phenomenon and its potential role in treatment outcome.

Napolitano et al. reported the occurrence of skin peeling in 11/916 (1.2%) patients under dupilumab, on average after the first dupilumab dose with transient aspect and complete spontaneous resolution within 7 days [4].

Similarly, Hammadi et al. described three cases of skin peeling occurring during dupilumab therapy for AD in adults. A 30-year-old man developed the manifestations on the face, trunk, flexures and extremities after the first dupilumab administration

with associated burning and hitching sensation. The clinical picture disappeared a week after, recurring with the second dose of dupilumab and disappearing spontaneously. Noteworthy, AD improved subsequently. A 33-year-old man with severe AD developed skin peeling a week after dupilumab administration on the same site of the previous patient, resolving spontaneously after 10 days, with further improvement of AD. A 26-year-old man presented skin peeling after about 4 days from dupilumab loading dose with prompt spontaneous resolution within 7 days, with subsequent resolution of AD. Overall, none of the patients displayed fever or photosensitivity, no novel drug introduction was recorded before clinical manifestations appeared [29]. Of note, the authors postulate that the occurrence of skin peeling anticipates the improvement in AD clinical manifestations, being regarded as a positive clinical biomarker for treatment response. Indeed, it has been supposed that dupilumab induces the replacement of the stratum corneum with healthy corneocytes able to restore a normal cutaneous barrier function. In support of this hypothesis, experiments in mouse model displayed that IL-4 is able to alter epidermal cohesion, decreasing the number of corneodesmosomes and downregulating desmoglein 1 in stratum corneum [29]. Overall, erythema and skin peeling are transient phenomena depending on dupilumab dosage, indeed manifesting mainly after the first loading dose, thus not requiring dupilumab discontinuation.

3.8. Red face or paradoxical erythema of the head and neck

Real-world data are increasingly showing the occurrence of paradoxical erythema of the head and neck during treatment with dupilumab [30]. Although this phenomenon, also called 'red face,' is becoming more widely described in the literature, its pathogenesis remains unclear. Interestingly, as reported in literature, the histopathology of such manifestations reveals the presence of a psoriasiform reaction pattern, in the absence of the histological hallmarks of AD, such as spongiosis, mononuclear and eosinophilic infiltrates. These histological findings are indicative of a drug-induced psoriasiform reaction rather than a pattern of AD.

Jo et al. reported the occurrence of dupilumab-associated facial or neck erythema in 101 patients affected by AD as a result of a review. Of them, 52 (52%) patients already presented with the involvement of face and neck at baseline, while 45 presented an AD phenotype that spared such areas. Referred associated symptoms included scaling, pruritus, pain and burning sensation. The occurrence of the adverse event ranged between 4 and 39 weeks from dupilumab start. In the management of red face, topical corticosteroids and inhibitors of calcineurin as well as systemic and topical antifungal agents were employed. Overall, 29 patients experienced improvements, while 4 demonstrated complete clearance. By contrast, 16 patients did not show any improvement, 8 worsened and 11 of them discontinued dupilumab for the scarce control of the red face notwithstanding specific treatment [31].

Overall, such adverse event is transient and does not require treatment discontinuation since it may be easily managed with topical and systemic treatments. Differential diagnoses include rosacea, allergic contact dermatitis, alcohol induced facial flushing, and *Malassezia*-related dermatitis. A possible pathogenetic role of *Malassezia furfur* in promoting cutaneous inflammation relies on the intrinsic lack of skin integrity barrier in patients with AD, leading to the yeast penetration into the skin provoking inflammation and the production of IgE specific anti-*Malassezia*. Hence, such biomarker may be employed to assess the role of such yeast in the head and neck phenotype of AD.

Russo et al. described the occurrence of red face in six patients with severe AD under dupilumab, occurring between 8 and 20 weeks from treatment initiation, with improvement of AD manifestations in the other areas of the body. No improvement was observed with topical anti-fungal treatment. Biopsies in line with literature data showed a psoriasiform pattern suggestive for drug reaction. Spontaneous resolution was observed with no treatment discontinuation [32].

3.9. Morphea

The occurrence of sclerosing diseases during treatment with dupilumab is paradoxical since Th2 cytokines have been shown to be important mediators involved in the pathogenesis of fibroproliferative disorders. Molecular studies underlined the role of IL-4 and IL-13 in promoting fibroblast chemotaxis and proliferation, production of collagen and extracellular matrix macromolecules. Consequently, their dysregulation could lead to exaggerated tissue repair and ultimately fibrotic disease, making the blockade of the IL-4/IL-13 axis a potential therapeutic approach as randomized placebo-controlled phase II studies investigating such topic are ongoing [33]. It seems that morphea is driven at early stages by Th1-mediated inflammation, and at later fibrotic stages by a Th2-mediated one [34]. The specific biomarkers involved in the process of morphea induced by dupilumab must still be addressed.

Interestingly, Kassamali et al. hypothesized the increased production of a pro-inflammatory splice variant of IL-4, IL-4 δ 2, as a consequence of IL-4 levels decline induced by dupilumab, that is able to promote the accumulation of T and B lymphocytes and the production of INF gamma and TNF alpha, responsible for boosted collagen production [35]. In their case report, a 20-year-old woman with AD recalcitrant to conventional treatments developed morphea 8 months after dupilumab initiation on upper and lower legs. The biological agent was withdrawn, and mycophenolate mofetil started with improvement of morphea manifestations after 7 months [35].

Wang et al. described the occurrence of morphea in two pediatric patients with AD under dupilumab [34]. A 10-year-old girl developed morphea of the inferior limb 34 months after dupilumab start that was followed by the biological agent discontinuation and administration of methotrexate and corticosteroids with improvement within 6 weeks. A 14-year-old boy experienced the appearance of morphea on the head earlier, at about 5 months of dupilumab treatment: after the drug discontinuation, topical and systemic corticosteroids, methotrexate and mycophenolate mofetil were prescribed unsuccessfully [34].

3.10. Rosacea-like eruptions

Sporadic cases of *Demodex* folliculitis, recurrent papulopustular rosacea eruption, and ocular rosacea-like disease during therapy with dupilumab have been rarely reported in the literature [36]. This immune dysregulation with alteration of Th1/Th2 balance via Th2 blockade, associated with possible impaired immune response against helminth infections, could explain the development of granulomatous rosacea-like eruption [37]. Anyway, the occurrence of rosacea-like folliculitis warrants further investigation.

Quint and colleagues described the occurrence of rosacea-like folliculitis in 6.4% ($n = 6/96$) of patients receiving dupilumab for AD. Onset time ranged from week 3 to 36. No information was specifically provided on the dupilumab discontinuation for such side effect [36].

Falcinelli et al. reported the occurrence of granulomatous rosacea in a 70-year-old man receiving dupilumab for severe AD after 3 years from treatment start. Manifestations occurred on the head and neck and the upper half of the trunk. Treatment with the biologic agent was discontinued and doxycycline administered (100 mg twice a day for 1 month) with complete resolution. Dupilumab was then restarted and re-stopped since the granulomatous manifestations recurred as soon as the first dose was administered [37].

4. Conclusion

The widespread use of dupilumab worldwide is highlighting the occurrence of novel adverse events, either cutaneous or extracutaneous, that will represent the utmost challenge for dermatologists in the long-term management of AD. The further investigation on their pathogenesis will improve the clinical management of patients and avoid the premature dupilumab discontinuation, especially when effective in treating AD.

5. Expert opinion

Dupilumab is currently approved for the treatment of many type-2 inflammatory diseases, including atopic dermatitis, with favorable safety profile since no routine laboratory monitoring is recommended. However, several cutaneous and extracutaneous adverse events have been reported in real-life setting, expanding the pool emerged from clinical trials. In detail, dupilumab may determine de-novo onset or exacerbation of preexisting conditions, whose pathogenesis is still unclear and seems to involve Th1/Th2 and Th2/Th17 immune-response imbalance.

In detail, AA, rosacea and vitiligo seem to be driven by the induced Th1 polarization of immune response; by contrast, in psoriasis and arthritis the Th17 axis displays to be prominently involved in the pathogenesis. Interestingly, morphea may be regarded as paradoxical phenomenon since the inhibition of IL-4 and IL-13 provides antifibrotic effect and is being studied as therapeutic approach at the late stage of disease. As for red face, the pathogenesis is still unclear and the role of *Malassezia* in the disease development has been proposed and need further investigation. Of note, skin peeling may be considered a positive prognostic factor for dupilumab response in AD, since it anticipates cutaneous clearance and

is transitory in the evolution. Indeed, the replacement of altered stratum corneum typical of patients with AD with healthy corneocytes able to restore a normal cutaneous barrier appears to be prompted by dupilumab. Concerning lymphomas, the increase in free IL-13 levels during dupilumab therapy determines the massive binding to IL-13 α 2 subunit receptor (IL-13Ra2) which has been shown involved in cell proliferation, invasion and immune evasion of several cancers. Hence, such AEs may be the result of the direct effect of the biological agent. Anyway, further investigation on the topic is warranted.

Overall, the management of dupilumab-induced adverse events must be evaluated case by case according to: a) drug efficacy for AD; b) severity of AEs; c) effective available treatments for the AEs; d) the transitory nature of the AEs; e) patients' satisfaction and expectations. Indeed, in cases where AEs are transitory and mild in severity dupilumab discontinuation should be discouraged and proper topical and systemic treatment administered. Contrarily, in case of neoplastic diseases or rapidly evolving and severe AEs, treatment withdrawal must be undertaken timely. In particular, as for lymphomas, the presence of an atypical AD phenotype (i.e. erythrodermic) should alert clinicians in performing a pretreatment biopsy with TCR gene rearrangement; also, even if biopsy rules out a neoplastic finding, a strict monitoring is recommended, especially when pruritus is uncontrolled. Moreover, since the occurrence of AEs is variable, ranging from soon after dupilumab initiation to several years, a long-term follow-up of patients must be carried out. Also, the potential reactivation of preexisting conditions makes crucial to conduct a thorough anamnesis before treatment commencement in order to foresee and early manage potential expected side effects. In the specific case of psoriasis, a positive family history should discourage the use of the biological agent in favor of other treatments that have a wider spectrum of action.

In our experience, the most frequently reported adverse events related to dupilumab therapy are facial redness and the appearance or worsening of psoriatic lesions. Specifically, in the presence of lesions involving the head and neck area in patients with atopic dermatitis undergoing biological therapy, a correct differential diagnosis must always be carried out. In fact, a concomitant allergic contact dermatitis often mediated by aeroallergens, as in the case of composites and sesquiterpenes, should be ruled out by performing patch tests. Although the majority of sensitizations are mediated by the type-1 immune response, treatment with dupilumab can influence the response to patch tests, which can be considered more reliable especially in cases in which this test has already been carried out previously.

In our clinical practice, in case of erythema of the head and neck area, the specific IgE dosage for malassezia is also performed, in order to exclude a form of hypersensitivity. As we know from recent literature, this dosage is useful both for predicting the risk of developing this adverse event and as an indicator of therapeutic response. Furthermore, in all cases it is necessary to collect a thorough anamnesis regarding the use of topical steroids in this area to exclude perioral dermatitis, rosaceiform reactions and erythematous lesions

associated with their chronic use. Hence, according to our experience, red face or facial redness related to dupilumab treatment becomes a diagnosis of exclusion; as for management, its transitory aspect, although the difficulty of an effective therapy, usually does not require treatment withdrawal.

Regarding the forms of psoriasis induced and/or aggravated by dupilumab, it is always important to investigate the personal and family history for this disease. In clinical practice, the severity of DAP or PsM can guide the management of these patients from the use of topical therapies and/or phototherapy, to immunosuppressants.

To conclude, it is important to conduct post-marketing studies in order to collect dupilumab-related AEs in real-life settings to improve patients' management in the view of a holistic approach. Also, the better understanding of AEs pathogenesis may increase clinicians' confidence and experience in tailoring patients' therapeutic approach.

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