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## **Review Article**

### ***Dupilumab-associated psoriasis and psoriasiform manifestations: a scoping review***

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**Short Title:** Review of dupilumab-associated psoriasis and psoriasiform manifestations

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**Key Message:** A review of psoriasiform eruption during treatment of with dupilumab in AD patients was performed.

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**Keywords:** dupilumab, psoriasis, atopic dermatitis, side effects

#### **Abstract**

**Background:** Dupilumab is the first approved IL-4R $\alpha$  inhibitor for the treatment of atopic dermatitis (AD) at present with good efficacy and safety. However, there have been several reports of psoriasis and psoriasiform manifestations occurring after dupilumab therapy in recent years, showing a new paradoxical cutaneous reaction associated with biologics.

**Summary:** This is a scoping review in order to summarize the demographics and epidemiology, clinical manifestations, diagnosis, potential pathogenesis, and promising management of dupilumab-associated psoriasis and psoriasiform manifestations (DAPs/PsM).

**Key Message:** The present review suggests that DAPs/PsM may occur in approximately 1.8-3.3% of AD patients after dupilumab therapy. In general, DAPs/PsM manifests similar clinical and histological features to classic psoriasis but not identical. T-cell polarization skewing between Th17 and Th2 spectrum may act as the core mechanism of DAPs/PsM, characterized by up-regulated IL-23/Th17 axis. Mild-to-moderate DAPs/PsM responds well to topical therapies while discontinuation of dupilumab is recommended in severe cases. Currently, JAK inhibitors and the combination of dupilumab with other biologics are considered as potential treatments for concurrent AD and psoriasis. Future researches are needed to clarify the detailed mechanism of this phenomenon in order to seek more effective management and prevention.

## Introduction

Dupilumab is a fully human monoclonal antibody that specifically targets for the alpha subunit of the interleukin-4 receptor (IL-4R $\alpha$ ), blocking both IL-4 and IL-13 signaling pathways, which are key mediators of Th2-mediated diseases such as atopic dermatitis (AD). Dupilumab is the first biologic agent approved for the treatment of AD since 2017. It has been also approved for asthma and chronic rhinosinusitis with nasal polyposis. Phase 3 trials and real-world studies suggested dupilumab could markedly relieve the signs and symptoms of AD and improve patients' quality of life [1, 2].

Dupilumab in treating patients with refractory AD and concomitant respiratory symptoms is extremely necessary due to the well-known atopic march theory, in which modifying the severity of AD might decrease the risk for the eventual development of asthma [3]. For AD in special population and anatomical sites, real-world studies have demonstrated that moderate-to-severe AD in the elderly and genital AD responded well to dupilumab therapy [4, 5]. Thus, dupilumab is gradually recommended as first-line treatment for uncontrolled AD in many countries and areas, providing a new therapeutic option for moderate-to-severe AD.

Although dupilumab is recommended for AD with significant therapeutic effects, the long-term postmarketing surveillance is needed to assess the safety of dupilumab. Most side effects of dupilumab are mild. Conjunctivitis, injection-site reactions, nasopharyngitis and headache are the most frequent side effects associated with dupilumab [1, 2, 6]. There have been other uncommon side effects associated with dupilumab reported in the literature. Tracey et al. reported the first case of dupilumab-associated erythrodermic psoriasis in 2018 [7]. Since then, more and more cases of psoriasis and psoriasiform manifestations associated with dupilumab have been reported in recent years, showing a latent side effect which is not discovered before in Phase 2 or 3 trials of dupilumab. Herein we conducted a literature review of dupilumab-associated psoriasis and psoriasiform manifestations (DAPs/PsM). A thorough search of literature was performed in the PubMed using the title search term [(Psoriasis\*) or (Psoriatic\*) or (Psoriasiform\*)] AND (dupilumab) from January 2018 to September 2022. Finally, 31 articles were found by hand-searching for “case report” or “case series”. The selected articles were full-text reviewed to make sure the contents of article relevant to DAPs/PsM. Results are summarized below and in Tables 1 and 2.

## Demographics and epidemiology of dupilumab-associated psoriasis and psoriasiform manifestations

Thirty-one articles comprising 47 patients (37 adults and 10 children) met our final inclusion criteria, including 44 patients with *de novo* psoriasis and 3 patients suffering the flare of pre-existent psoriasis after dupilumab treatment (Table 1). For *de novo* psoriasis, the average age of patients is 48.6 years old (range, 22-92 years old) in adult group, with a roughly equivalent number of males and females (Table 2). The mean time to onset of *de novo* psoriasis after dupilumab treatment is 4.3 months (range, 1-18 months) in adult, roughly consistent with previous studies [24, 38-40]. The mean time to onset in pediatric patients is slightly longer than adults (6.4 months, range from 2-12 months). Besides, the flare of pre-existent psoriasis after dupilumab treatment presents a relatively shorter onset-time of 3.3 in average (n=3). Most of patients (93.6%, 44/47) developed psoriasis or psoriasiform manifestations after initiation of dupilumab within 1 year, suggesting the first year of dupilumab treatment should be kept closely monitoring and following up by clinicians. However, there were some cases showing a long onset-time of 1.5 years or even 2.5 years [9, 27], the exact cause of long onset-time is unclear, but a long-term follow-up after dupilumab treatment is recommended.

## Dupilumab-associated psoriasis and psoriasiform manifestations versus Classic psoriasis

The largest cohort study performed by Jaulent et al. showed a 1.88% (7/373) incidence of DAPs/PsM [38], while Napolitano et al. suggested an incidence of 3.33% (3/90) in 2019 and 3.03% (5/165) in 2021 [2, 12]. These reported numbers seemed similar with the prevalence rate of classic psoriasis in the general population. However, it's hard to determine whether individuals with DAPs/PsM have the same genetic risk as general population, due to the variable prevalence rate of psoriasis in different region ranging from 0.36% to 2.73% [41]. Surprisingly, a recent retrospective review of dupilumab for AD and dermatitis not otherwise specified (DNOS) showed a high incidence of

psoriasis up to 7.0% (14/199), and 43% (6/14) patients with DAPs/PsM in this cohort had a distant history of psoriasis prior to starting dupilumab for AD/DNOS [42]. The history of psoriasis may explain such a high incidence of psoriasis in this cohort, and this result reminds us that dupilumab is not recommended to patients who have history of psoriasis.

#### ***Dupilumab-associated psoriasis and psoriasiform manifestations versus Concomitant AD and psoriasis***

AD and psoriasis were once considered as mutually antagonistic diseases because this required the activation of opposing inflammatory pathways [43]. However, there are many reports and systematic reviews that shows AD and psoriasis can coexist in the same individuals, both simultaneously and/or consecutively. Cunliffe et al. in a systematic review found the prevalence of AD in those with psoriasis valued from 0.17% to 20% (pooled prevalence 2%), while the prevalence of psoriasis in those with AD ranged from 0.3% to 12.6%, with a pooled prevalence of 2% [44]. Barry et al. also reported the prevalence of concomitant AD and psoriasis was 1.3% of the total population of patients diagnosed with either psoriasis or AD [45], and the number was pretty close to the incidence of DAPs/PsM mentioned above (range from 1.88%-3.33%). In fact, systemic therapies may be a trigger to promote the processes that AD patients develop psoriasis or psoriasis patients develop AD. These processes can also happen regardless of whether undergoing systemic or topical therapies [46]. Thus, we hypothesize that dupilumab may act as a possible triggering factor, but not a decisive factor, to promote AD patients develop psoriasis. This can explain why the prevalence of DAPs/PsM in patients with AD is roughly equal but slightly higher than the prevalence of concomitant AD and psoriasis.

In summary, the incidence of DAPs/PsM is at a relatively low level, and almost equal to the prevalence of classic psoriasis and (or) concomitant AD and psoriasis. This result may imply that the occurrence of psoriasiform manifestations is dominated by intrinsic factors, and dupilumab contributes to the process as an extrinsic trigger.

#### **Clinical manifestations of dupilumab-associated psoriasis and psoriasiform manifestations** ***de novo Psoriasis: General psoriasiform manifestations associated with dupilumab***

In general, DAPs/PsM shows similar clinical features to classic psoriasis in many aspects. Plaque psoriasis (77.1% in adult and 100% in children) was the most common subtype of psoriasis reported in previous studies, which also accounts for the largest proportion of cases in classic psoriasis. The dupilumab-associated psoriatic plaques were often described as well-demarcated erythematous scaly plaques, showing no difference from classic psoriatic plaques in appearance. Guttate, erythrodermic, and pustular psoriasis have also been reported [7, 11, 17, 20, 31, 32, 34, 35], accounting for a small proportion. However, Jaulent et al. reported a high proportion of pustular psoriasis (43%, 3/7) as a specific clinical feature in DAPs/PsM [38]. Some specific variants of psoriasis, such as reverse psoriasis and sebopsoriasis, could also occur in patients with dupilumab therapy [22, 30]. Sebopsoriasis, as a combination of psoriasis and seborrheic dermatitis, was thought to result from the abnormal immune response to *Malassezia* induced by cytokine imbalances due to dupilumab [22].

Extremities (77.1% in adult and 77.8% in children) were the most common onset sites, especially bilateral extensor surfaces of upper and lower extremities, consistent to classic psoriasis. Additionally, trunk (37.1%) and scalp (31.4%) were other common locations in adults, while pediatric psoriasis was more common in face and neck (55.6%). Palmoplantar and nail psoriasis have also been reported, occurring alone or in combination with lesions elsewhere [9, 20, 25, 28]. Recently, Fan et al. reported a case of reverse psoriasis occurring in armpits, indicating that flexural and intertriginous areas could also be affected by DAPs/PsM, especially easy to be confused with pre-existing AD [30]. Psoriatic plaques were mostly noticed in areas of skin that had not been affected by AD before, but a few cases revealed that psoriasis appeared on the original lesions, switching from AD to psoriasis directly [14, 32].

Scalp lesions were especially frequent in DAPs/PsM. Interestingly, alopecia areata (AA) could also be triggered by dupilumab, even coexisting with DAPs/PsM in scalp [24]. Two different patterns of dupilumab-associated alopecia were described: classic AA and psoriatic alopecia plaques (AA-like

reactions) associated with erythemas and scales. Psoriatic alopecia plaques could be confirmed by biopsy to distinguish from AA if necessary.

#### ***Flare of pre-existent psoriasis: A more severe attack***

In theory, it's unconventional that dupilumab should be applied to patients with psoriasis, but this condition can happen occasionally when pre-existent psoriasis is misdiagnosed or mixed up with AD. Herein, we presented three cases of the flare of pre-existent psoriasis. The earliest case reported a patient with probable pre-existent psoriasis has developed into severe erythrodermic psoriasis after dupilumab therapy [7]. And the other cases showed a persistent or enlarged psoriatic plaques at the original site [35, 37]. These cases illustrated that dupilumab can indeed induce the flare of pre-existent psoriasis, with more severe lesions and shorter time to onset (3.3 months in average compared with 4.3 months in *de novo* psoriasis).

#### **Clinical diagnosis of dupilumab-associated psoriasis and psoriasiform manifestations**

The clinical diagnosis of DAPs/PsM was mainly based on typical psoriasiform lesions and the temporal relationship between dupilumab treatment. A full body examination should be checked for DAPs/PsM, particularly in areas of scalp, palms, soles, and nails. For pediatric patients, face, neck, and pubic area should also be examined carefully. A case of dupilumab-induced acute generalized exanthematous pustulosis (AGEP) on the second day after initiation of dupilumab was reported recently [47], suggesting that the clinical history is also crucial for differential diagnosis of AGEP and dupilumab-associated generalized pustular psoriasis.

Skin biopsy can be helpful to diagnose DAPs/PsM, but rarely performed in pediatric patients when diagnosis and empiric treatment were allowed. The histopathological features of DAPs/PsM were not always consistent with classic psoriasis in some cases, showing an overlapping psoriasiform/spongiotic feature [14]. Classic psoriatic histopathological features include parakeratosis, hyperkeratosis, acanthosis of the epidermis, dilated capillaries, and lymphocytic infiltration in the dermis. These features were often found in DAPs/PsM, while mild spongiosis was also reported [14, 23, 25]. The overlapping psoriasiform/spongiotic feature may suggest that psoriasiform lesions associated with dupilumab still have a Th2-predominant background [48]. In addition, the occasional presence of eosinophils and (or) plasma cells has been reported in psoriasiform plaques induced by TNF- $\alpha$  inhibitors. It was considered as a clue to distinguish it from classic psoriasis, which also might be helpful to identify DAPs/PsM [49]. Interestingly, non-psoriasiform lesions clinically could present psoriasiform changes histologically in some cases. de Wijs et al. reported a case series of dupilumab-associated paradoxical head and neck erythema with less or no scaling, markedly different from psoriasis in clinical appearance; but histopathology showed epidermal hyperplasia, increased dilated capillaries, and a perivascular lymphocytic infiltration, suggesting psoriasiform changes [50].

In practice, differentiation between psoriasis and AD lesions can be difficult in some cases, both clinically and histologically, especially if areas as the scalp or hand/feet are affected. Therefore, it's a challenge for dermatologists to identify DAPs/PsM at an early stage, and a comprehensive judgment of clinical history, manifestations and histopathology is crucial for clinicians to diagnose DAPs/PsM.

#### **Pathogenesis of dupilumab-associated psoriasis and psoriasiform manifestations**

##### ***Th2 and Th17-mediated disease: Two poles of one spectrum***

Psoriasis and AD are both non-communicable inflammatory skin diseases mediated by T cells, cytokines, chemokines, and other cells of the immune system. In skin, T cells differentiate into specific subsets in response to distinct cytokines, then secrete cytokines to drive epidermal keratinocytes to alter growth and differentiation patterns, leading to the outcome of different inflammatory skin diseases [51]. Psoriasis is an inflammatory skin disease featured by Th1/Th17 cells with increased TNF- $\alpha$ , IL-17 and IL-23; while AD is a mainly Th2-mediated disease, involving increased IL-4, IL-5, and IL-13 [52]. Recent studies have found that psoriasis and AD are not isolated diseases but two opposite poles of the same Th17-Th2 cell polarization spectrum where T cells can present variably polarization degrees and create some overlapping disease characteristics [53]. Moreover, blocking Th1 and Th17 pathways may result in the occurrence of Th2-mediated diseases. Paolino et al. reported a case series of psoriatic patients developed AD and/or eczematous-like eruptions after

biologic treatments (4 patients with ustekinumab, 2 patients with adalimumab, 1 patient with ixekizumab, and 1 patient with guselkumab) [46]. Similarly, blocking of Th2 pathway may lead to T-cell polarization shift to Th17 subsets, explaining the phenomenon of DAPs/PsM in AD patients [7]. A recent unusual case reported secukinumab-induced AD in a patient with psoriasis that had resolved following several months of treatment with dupilumab, but subsequently these patients had developed re-emergence of psoriatic lesions with dupilumab therapy [54]. These evidences strongly suggests that Th17 and Th2 pathways are one spectrum where immune conditions can reversibly switch from one pole to the other with the trigger of biologic therapy.

Psoriasis induced by dupilumab is not an accidental phenomenon. A large number of cases was provided to support that IL-4/IL-13 axis may act as a restraint toward Th17 pathway activation in some organs, and IL-4/IL-13 blockers may lead an increased incidence of Th17-type disease (such as enthesitis/enthesopathy, seronegative arthritis, spondyloarthropathy, uveitis, psoriasis and nail psoriasis) [55]. Interestingly, ankylosing spondylitis (AS) and inflammatory bowel disease (IBD), parts of the Th17 diseases, are not associated with dupilumab therapy [55]. Thus, further immunology studies are needed to refine the Th2-Th17 spectrum and related comorbidities driven by cytokines.

#### ***IL-23/IL-17: The key target of immune shift***

Recent experimental studies have reported an increased IL-23A and *de novo* IL-17A expression in DAPs/PsM, suggesting the remarkable activation of IL-23/Th17 axis in psoriasiform lesions [23, 56]. The *de novo* IL-17A level of DAPs/PsM was even higher than classic psoriasis, suggesting a strong shift to Th17 induced by dupilumab. It is well-known that IL-4 is a cytokine capable of negatively affecting Th17 lymphocyte function and upstream IL-23 production secreted by antigen-presenting cells [57]. Bridgewood et al. also found that human enthesis contains IL-23-producing cells, and the production of IL-23 is attenuated by IL-4 and IL-13 treatment *in vitro* studies [58]. Thus, IL-4/IL-13 blockers may increase IL-23 and downstream IL-17 production and consequently trigger Th17-mediated diseases. IL-17 may act as the crucial intrinsic factor to activate Th17-mediated inflammation, which can be artificially up-regulated by extrinsic IL-4/IL-13 blockers (dupilumab). Thus, patients with a high level of intrinsic IL-17 may be hypersensitive to DAPs/PsM. Specific subtypes of AD, including Asian and pediatric patients, have a prominent IL-17 component [53]. A case of Asian (Chinese) teenage twin brothers with a long history of AD since childhood has been reported. The twin brothers developed psoriasiform erythemas under the treatment of dupilumab, with a high IL-17A expression [36]. This result may indicate that Asian and pediatric patients have a higher possibility to develop DAPs/PsM because of the intrinsic Th17 component. Similarly, Flanagan et al. summarized 18 cases of DAPs/PsM and found that most patients (83%) had AD since childhood, suggesting chronic AD is also more likely to develop psoriasis due to a partial Th1/Th17 shift in chronic AD [29]. However, more strong evidences are needed to support that Asian, pediatric, and chronic AD patients have a higher incidence of DAPs/PsM than other patients.

In addition, DAPs/PsM had a higher IL-4 expression compared with classic psoriasis [56], and the IL-13 level was decreased after dupilumab treatment but not absent during the onset of DAPs/PsM in AD patients [23]. These results support that DAPs/PsM has a Th2 immune background, consistent to the specific histological features mentioned above. The coexistence of high IL-17/IL-23 and persistent IL-4/IL-13 expression seems paradoxical, but reflect that DAPs/PsM is an inflammatory disease based on a specific intermediate state of Th2-Th17 spectrum both histologically and immunologically. Besides the mechanism of T-cell polarization skewing, the common environmental factors and genetic backgrounds shared by AD and psoriasis may also contribute to the occurrence of DAPs/PsM. A population-based study by Simpson et al. has found that Th1- and Th2-mediated diseases share common environmental risk factors to increase the likelihood of Th1 or Th2-mediated immune response to nonspecific antigens [59]. Furthermore, a recent genome-wide study confirmed a high degree of genomic coincidence between AD and psoriasis, suggesting the overlapping of genetic backgrounds in these two diseases [60].

In summary, the T-cell polarization skewing theory may act as the key point of DAPs/PsM, and shared environmental and genetic factors between AD and psoriasis are involved. The disinhibition of IL-23/IL-17 axis suppressed by IL-4 can partly explain the occurrence of DAPs/PsM. However, many

relevant questions, including the no correlation between partial Th17 diseases (IBD and AS) and dupilumab, and whether patients with higher IL-17 component are hypersensitive to DAPs/PsM, are still not completely clear. Thus, more studies are needed to help us deepen the understanding of dupilumab to guide the clinical application in the future.

#### **Management and prevention of dupilumab-associated psoriasis and psoriasiform manifestations**

At present, there is no high-quality evidence-based management guideline for DAPs/PsM. However, as a specific paradoxical reaction induced by the monoclonal antibody, the treatments can roughly refer to guidelines of classic psoriasis and other paradoxical reactions [39]. The aim of management is to alleviate psoriasiform lesions while maintaining control of AD, so weighing the severity of DAPs/PsM against the therapeutic effects of AD is essential in management.

#### **General practical guidelines for de novo psoriasis**

For mild-to-moderate DAPs/PsM, topical therapies, phototherapy, and even systemic therapies can be considered. Discontinuation of dupilumab may not be necessary. Topical glucocorticoids (84.4%) or combinations of glucocorticoids and vitamin D derivatives (18.8%) were widely applied to these patients, consistent to the preferred conventional treatments of mild classic psoriasis. Phototherapy (narrow-band UVB) [12, 14], and systemic therapies (oral steroids [12, 21, 26, 34], cyclosporine [21, 28, 32], mycophenolate mofetil [23]) were also reported for the treatment of mild-to-moderate DAPs/PsM. Most patients' psoriasiform lesions could be completely cleared or partly improved after sufficient topical therapies. Parker et al. suggested that DAPs/PsM in pediatric patients might be less refractory than adults. Psoriasiform lesions could achieve acceptable clearance with topical glucocorticoids in all pediatric patients without discontinuation of dupilumab [35]. Ustekinumab, an IL-12/ IL-23 inhibitor, has also been applied in a pediatric patient [35], but whether recommending it as the first-line treatment of DAPs/PsM should be prudent considering the high cost for drugs and potential side effects.

For severe DAPs/PsM, discontinuation of dupilumab is recommended. We found that 48.5% adult patients chosen discontinuation of dupilumab and their psoriasiform lesions achieved various degrees of remission after discontinuation or combinations of discontinuation and additional treatments. Restarting of dupilumab after discontinuation is generally not advised due to the high risk of psoriasis recurrence. Kim et al. reported a case of the recurrence of DAPs/PsM after restarting dupilumab, suggesting the recurrent and refractory features of DAPs/PsM [16].

#### **Innovative treatments for concurrent psoriasis and AD**

Currently, Janus Kinase (JAK) inhibitors are considered as potential treatments for patients presenting both AD and psoriasis, providing new ideas for the treatment of refractory DAPs/PsM [38]. Baricitinib, an oral selective JAK1 and JAK2 inhibitors, was applied to two seventeen-year-old teenagers with DAPs/PsM and showed a significant reduction in skin lesions [36]. Upadacitinib (selective JAK 1 inhibitor), was also reported in treating DAPs/PsM, resulting complete remission of both psoriasiform eruptions and AD [33]. For topical treatments, Kurihara et al. reported two cases of DAPs/PsM achieved remarkable improvement with the delgocitinib ointment after ineffective remission of topical corticosteroids and 0.1 % tacrolimus ointment [27].

The combination of dupilumab with other monoclonal antibodies is another promising therapy strategies for concurrent psoriasis and AD. A short-term retrospective studies reviewed six patients treated with biologic combination therapies (dupilumab and guselkumab), and found almost all of the patients (83.3%, 5/6) have presented significant improvement in both AD and psoriasis [61]. The safety of dupilumab associated with other monoclonal antibodies appears to be an important issue. Further studies summarized case reports of dupilumab in combination with other biologics (such as guselkumab, secukinumab, adalimumab, benralizumab, omalizumab, etc.), presenting no or mild adverse drug reactions for a 2-22 months period of observation [62]. However, long-term monitoring is necessary to evaluate the safety of biologics in combination. The cost of multiple biologics is also of concern in clinical practice.

The principal prevention of DAPs/PsM is to strictly control the indications of dupilumab. Family or personal history of psoriasis may be risk factors for the occurrence and severity of psoriasis eruptions

[12, 13], so dupilumab is not recommended for these patients. Furthermore, a long-term follow-up after initiating dupilumab therapy is especially important.

#### **Conclusion**

Dupilumab-associated psoriasis and psoriasiform manifestations are relatively rare side effects triggered by dupilumab, mainly related to T-cell subsets imbalance and multiple factors. This phenomenon is also a supplement of paradoxical reaction induced by biologic agents, providing strong evidences of that AD and psoriasis are two poles of the same Th17-Th2 cell polarization spectrum. Clinicians should improve the awareness of this phenomenon while dupilumab is widely used in clinical practice worldwide in recent years. Future researches are needed to clarify the detailed mechanism of dupilumab-associated psoriasis and psoriasiform manifestations in order to seek more effective management and prevention.

**Conflict of Interest Statement**

The authors have no conflicts of interest to declare.

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**Author Contributions**

Zheng Su wrote the draft of the manuscript. Yue-Ping Zeng M.D. supervised the work and revised the manuscript for critical revision.

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**Table 1** Case reports and cases series of dupilumab-associated psoriasis and psoriasiform manifestations

| References                                 | Age<br>(year) | Gender | Duration <sup>a</sup><br>(month) | Family<br>history <sup>b</sup> | Type          | Localization                                                                       | Histological examination                                                                                                                                                                                                                                                                                    | Dupilumab<br>interruption | Management                                                | Outcome                |
|--------------------------------------------|---------------|--------|----------------------------------|--------------------------------|---------------|------------------------------------------------------------------------------------|-------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|---------------------------|-----------------------------------------------------------|------------------------|
| <i>de novo Psoriasis in Adult Patients</i> |               |        |                                  |                                |               |                                                                                    |                                                                                                                                                                                                                                                                                                             |                           |                                                           |                        |
| Safa, 2019 [8]                             | 55            | M      | 2                                | No                             | Plaque        | Trunk                                                                              | Parakeratosis, hyperkeratosis, acanthosis, dilated capillaries and lymphocytic infiltrate in the upper dermis, consistent with psoriasis                                                                                                                                                                    | No                        | Topical steroids                                          | Improvement            |
| Fowler, 2019 [9]                           | 54            | F      | 4                                | NA                             | Plaque        | Bilateral upper and lower extremities, chest, back, neck, abdomen, soles and palms | Acute spongiotic dermatitis with lymphocyte exocytosis                                                                                                                                                                                                                                                      | Yes                       | NA                                                        | Improvement            |
|                                            | 49            | F      | 18                               | NA                             | Plaque        | Bilateral upper and lower extremities, nail                                        | NA                                                                                                                                                                                                                                                                                                          | No                        | Topical clobetasol                                        | Improvement            |
| Stout, 2019 [10]                           | 59            | F      | 1                                | NA                             | Plaque        | Bilateral upper and lower extremities                                              | Confluent parakeratosis with absent granular cell layer, regular acanthosis, and thinning of the suprapapillary plates, consistent with classic psoriasis vulgaris                                                                                                                                          | Yes                       | Topical triamcinolone                                     | Improvement            |
| Gori, 2019 [11]                            | 40            | F      | 3.5                              | No                             | Guttate       | Trunk and extremities                                                              | Parakeratosis, hyperkeratosis, acanthosis, dilated capillaries and a lymphocytic infiltrate in the upper dermis                                                                                                                                                                                             | No                        | Topical calcipotriol betamethasone                        | Improvement            |
| Napolitano, 2019 [12]                      | 74            | F      | 6                                | No                             | Plaque        | Scalp                                                                              | Parakeratosis, hyperkeratosis, Munro microabscess and inflammatory dermal infiltrate composed mainly by lymphoplasma cells                                                                                                                                                                                  | No                        | Clobetasol lotion                                         | Improvement            |
|                                            | 50            | M      | 5                                | No                             | Plaque        | Scalp, hands and upper limbs                                                       | Hyperkeratosis, parakeratosis, psoriasiform hyperplasia, and dermal infiltrate composed mainly by T lymphocytes and neutrophils                                                                                                                                                                             | No                        | Calcipotriene/ betamethasone foam                         | Improvement            |
|                                            | 32            | M      | 1                                | Yes                            | Plaque        | Hands, trunk and lower limbs                                                       | Parakeratosis, hyperkeratosis, Munro microabscess and dermal infiltrate of lymphocytes, macrophages and neutrophils                                                                                                                                                                                         | Yes                       | Clobetasol ointment, Prednisone tablets NB-UVB            | Insufficient remission |
| Varma, 2020 [13]                           | 73            | M      | 1                                | NA                             | Plaque        | Bilateral forearms and right leg                                                   | NA                                                                                                                                                                                                                                                                                                          | NA                        | NA                                                        | NA                     |
| Schrom, 2020 [14]                          | 80            | M      | 2.5                              | NA                             | Plaque        | Trunk, arms, lower extremities                                                     | Orthokeratosis overlying parakeratosis, very mild spongiosis, lymphocyte exocytosis, and a mild superficial perivascular lymphocytic infiltrate                                                                                                                                                             | Yes                       | NB-UVB                                                    | Improvement            |
| Ferrucci, 2020 [15]                        | 42            | M      | 3                                | No                             | Plaque        | Trunk and limbs                                                                    | Histological diagnosis of psoriasis                                                                                                                                                                                                                                                                         | Yes                       | Topical calcipotriene and betamethasone dipropionate foam | Improvement            |
| Kim, 2020 [16]                             | 36            | F      | 5                                | No                             | Plaque        | Knees and shins                                                                    | Hyperkeratosis with confluent parakeratosis, uniformly elongated rete ridges, the absence of the granular layer, thinning of the supra-papillary plates and collections of neutrophils in the stratum corneum consistent with Munro’s micro-abscesses, a superficial perivascular infiltrate of lymphocytes | Yes                       | Topical clobetasol propionate 0.05%                       | Recurrence             |
| Gambichler , 2020 [17]                     | 59            | M      | 1                                | NA                             | Erythrodermic | Extremities                                                                        | Psoriasiform hyperplasia with decreased granular layer and focal parakeratosis, mainly perivascular lymphocytic infiltrates in the dermis                                                                                                                                                                   | Yes                       | NA                                                        | NA                     |
| Matsuda, 2020 [18]                         | 60            | M      | 3.5                              | NA                             | Plaque        | Knees, right condyle to hands, elbows, face                                        | Hyperkeratosis, thinning and disappearance of the stratum, granulosum, and neutrophilic infiltration into the stratum corneum                                                                                                                                                                               | Yes                       | Topical steroids                                          | Improvement            |
| DeGrazia, 2020 [19]                        | 32            | F      | 1                                | No                             | Plaque        | Scalp, bilateral inguinal folds                                                    | NA                                                                                                                                                                                                                                                                                                          | No                        | Topical steroids                                          | NA                     |
|                                            | 67            | M      | 2                                | No                             | Plaque        | Scalp                                                                              | NA                                                                                                                                                                                                                                                                                                          | No                        | Topical steroids                                          | NA                     |

|                      |    |   |     |    |            |                                                                 |                                                                                                                                                                                                                                                                 |     |                                                                          |             |
|----------------------|----|---|-----|----|------------|-----------------------------------------------------------------|-----------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|-----|--------------------------------------------------------------------------|-------------|
|                      | 57 | F | 9   | No | Plaque     | Scalp                                                           | NA                                                                                                                                                                                                                                                              | No  | Topical steroids                                                         | NA          |
| D'Ambra, 2020 [20]   | 61 | F | 1   | No | Guttate    | Trunk and extremities                                           | NA                                                                                                                                                                                                                                                              | No  | Clobetasol propionate cream                                              | Improvement |
|                      | 56 | F | 2   | No | Plaque     | Scalp, elbows, arms                                             | Hyperplastic epidermis with papillomatosis, hypogranulosis, parakeratosis and presence of neutrophils in the corneum layer, a slight perivascular lymphocytic infiltrate in the upper dermis                                                                    | No  | Calcipotriene/betamethasone dipropionate foam                            | Improvement |
|                      | 39 | M | 1   | No | Plaque     | Soles                                                           | NA                                                                                                                                                                                                                                                              | No  | Topical corticosteroids                                                  | Improvement |
| Senner, 2020 [21]    | 40 | M | 1.5 | NA | Plaque     | Lower limbs and palms                                           | Acanthosis, papillomatosis, extensive loss of stratum granulosum and parakeratosis, presence of neutrophils in the epidermis; an edema, meandering capillaries and a lymphocytic infiltrate in the stratum papillary                                            | Yes | Topical steroids, oral prednisone, topic salicylic acid, cyclosporine    | Improvement |
| Al-Janabi, 2020 [22] | 72 | M | 4   | No | Seborrheic | Scalp, eyebrows, external auditory meatus                       | NA                                                                                                                                                                                                                                                              | No  | Clobetasol propionate, salicylic acid 0.5%, distilled coal tar 1%        | Improvement |
| Mirza, 2021 [23]     | 92 | M | 8   | NA | Plaque     | Extremities                                                     | Acanthosis, parakeratosis with abundant neutrophils, loss of the granular cell layer, minimal spongiosis, dilated capillary loops in the papillary dermis and a perivascular lymphocyte predominant inflammatory infiltrate                                     | No  | Mycophenolate mofetil                                                    | Improvement |
| Beaziz, 2021 [24]    | 45 | F | 12  | No | Plaque     | Scalp                                                           | NA                                                                                                                                                                                                                                                              | No  | Topical clobetasol propionate 0.05%                                      | Improvement |
| Maiolini, 2021 [25]  | 22 | M | 5   | NA | Plaque     | Vertex region, left wrist and toes, nail pitting in the fingers | Psoriasiform dermatitis with confluent parakeratosis, spongiosis, exocytosis of lymphocytes and extravasated red blood cells                                                                                                                                    | NA  | Topical betamethasone dipropionate and calcipotriol                      | Improvement |
| Russo, 2021 [26]     | 68 | F | 1   | NA | Plaque     | Arms and buttocks                                               | Acanthosis, elongation of the epidermal rete ridges, parakeratosis associated with hypogranulosis, sterile intracorneal and subcorneal pustules, lymphohistiocytic and neutrophilic infiltrate in the edematous dermis, subcorneal spongiform pustules of Kogoj | Yes | Oral corticosteroids                                                     | Improvement |
| Kurihara, 2021 [27]  | 34 | M | 30  | NA | Plaque     | Arms and trunk                                                  | Psoriasiform acanthosis with a diminished granular layer and intracorneal microabscesses within a parakeratotic scale                                                                                                                                           | No  | Topical corticosteroids, tacrolimus ointment 0.1%, delgocitinib ointment | Improvement |
|                      | 23 | M | 18  | NA | Plaque     | Face                                                            | Psoriasiform acanthosis with intracorneal microabscesses                                                                                                                                                                                                        | No  | Topical corticosteroids, tacrolimus ointment 0.1%, delgocitinib ointment | Improvement |
| Park, 2021 [28]      | 24 | M | 2   | NA | Plaque     | Palms and soles                                                 | Hyperkeratosis, parakeratosis, diffuse hypogranulosis, regular rete ridge elongation, suprapapillary thinning                                                                                                                                                   | No  | Topical corticosteroids                                                  | Improvement |
| Flanagan, 2022 [29]  | 28 | F | 5   | No | Plaque     | Scalp, abdomen, proximal extremities                            | NA                                                                                                                                                                                                                                                              | Yes | Topical clobetasol                                                       | Improvement |
| Fan, 2022 [30]       | 25 | F | 2   | No | Reverse    | Armpits                                                         | NA                                                                                                                                                                                                                                                              | Yes | Topical hormonal cream, compound glycyrrhizin                            | Improvement |
| Uysal, 2022 [31]     | 22 | M | 4   | No | Pustular   | Dorsal hands                                                    | Regular, psoriasiform acanthosis and parakeratosis of the epidermis with elongated rete ridges; subcorneal spongiotic pustule of neutrophil leucocytes, consistent with pustular psoriasis                                                                      | Yes | Topical corticosteroid and calcipotriol                                  | Improvement |
| Jia, 2022 [32]       | 23 | M | 2   | NA | Pustular   | Lower legs                                                      | Parakeratosis, hyperkeratosis, epidermal hyperplasia, dilated capillaries, and lymphocyte infiltrate in the upper dermis; dense neutrophil infiltration in the stratum corneum and subcorneal zone forming spongiform abscesses                                 | Yes | Topical steroids, cyclosporine                                           | Improvement |

|                                                      |           |   |      |     |                     |                                                                  |                                                                                                                                                                                                                              |     |                                                                                            |             |
|------------------------------------------------------|-----------|---|------|-----|---------------------|------------------------------------------------------------------|------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|-----|--------------------------------------------------------------------------------------------|-------------|
| Patruno, 2022 [33]                                   | 58        | F | 5.5  | Yes | Plaque              | Scalp, hands, and legs                                           | Acanthosis, parakeratosis, exocytosis, hypogranulosis, dermal inflammatory infiltrate composed mainly of lymphoplasma cells, T lymphocytes and Langerhans cells and/or neutrophils, dilated vessels of the superficial derma | Yes | Upadacitinib                                                                               | Improvement |
| Zhong, 2022 [34]                                     | 51        | F | 2    | No  | Pustular            | Arms and trunk                                                   | Parakeratosis, psoriatic hyperplasia, dilated tortuous vessels in the papillary dermis; The superficial dermis was infiltrated by large quantities of perivascular lymphocytes and neutrophils                               | Yes | Methylprednisolone                                                                         | Improvement |
| de novo Psoriasis in Pediatric Patients              |           |   |      |     |                     |                                                                  |                                                                                                                                                                                                                              |     |                                                                                            |             |
| Parker, 2021 [35]                                    | 4         | M | 9-12 | No  | Plaque and Pustular | Trunk and legs                                                   | NA                                                                                                                                                                                                                           | Yes | Topical corticosteroid, ustekinumab                                                        | Improvement |
|                                                      | 14        | F | 8    | No  | Plaque              | Face and neck                                                    | NA                                                                                                                                                                                                                           | No  | Triamcinolone 0.1% ointment                                                                | Improvement |
|                                                      | 12        | F | 10   | No  | Plaque              | Extensor knees                                                   | NA                                                                                                                                                                                                                           | No  | Mometasone 0.1% ointment                                                                   | Improvement |
|                                                      | 18        | M | 7    | No  | Plaque              | Scalp, forehead, neck                                            | NA                                                                                                                                                                                                                           | No  | Triamcinolone 0.1% ointment, betamethasone dipropionate shampoo, clobetasol 0.05% solution | Improvement |
|                                                      | 16        | M | 7    | No  | Plaque              | Left ankle, right knee                                           | NA                                                                                                                                                                                                                           | No  | Mometasone 0.1% ointment                                                                   | Improvement |
|                                                      | 18        | F | 6    | No  | Plaque              | Abdomen, pubic area, ears, neck, and arms                        | NA                                                                                                                                                                                                                           | No  | Triamcinolone 0.1% ointment, pimecrolimus cream                                            | Improvement |
| Park, 2021 [28]                                      | 17        | M | 2    | NA  | Plaque              | Palms and soles                                                  | Hyperkeratosis, parakeratosis, multifocal hypogranulosis, regular rete ridge elongation                                                                                                                                      | Yes | Cyclosporine                                                                               | Improvement |
| Ali, 2022 [36]                                       | 17 (twin) | M | 5    | No  | Plaque              | Scalp, face, abdomen, back, upper and lower extensor extremities | psoriasiform hyperplasia, ectatic capillaries, perivascular lymphocytes infiltration acanthosis with thinning of suprapapillary plates, confluent parakeratosis with the absence of the granular cell layer                  | Yes | Baricitinib                                                                                | Improvement |
| Dupilumab-associated Flare of Pre-existent Psoriasis |           |   |      |     |                     |                                                                  |                                                                                                                                                                                                                              |     |                                                                                            |             |
| Tracey, 2018 [7]                                     | 50        | F | 2    | NA  | Erythrodermic       | Scalp, Trunk, bilateral upper and lower extremities              | Psoriasiform hyperplasia with diminished granular layer and parakeratotic scale (arm); Acanthosis, mild spongiosis, and intraepidermal neutrophils forming subcorneal pustules (abdomen)                                     | Yes | Methotrexate, topical steroids                                                             | Improvement |
| Dimitrov, 2020 [37]                                  | 35        | M | 5    | NA  | Plaque              | Forehead, arms, lower leg                                        | Characteristic changes of psoriasis                                                                                                                                                                                          | NA  | NA                                                                                         | NA          |
| Parker, 2021 [35]                                    | 9         | F | 3    | NA  | Plaque              | Elbows                                                           | NA                                                                                                                                                                                                                           | No  | Betamethasone dipropionate ointment 0.05%                                                  | Improvement |

<sup>a</sup> Time from dupilumab treatment to onset of psoriasis.

<sup>b</sup> Family history of psoriasis.

F: female, M: male, NA: Not available.

**Table 2** Clinical characteristics of *de novo* psoriasis associated with dupilumab <sup>a</sup>

| Characteristics                         |                          |
|-----------------------------------------|--------------------------|
| <b>Gender</b>                           | <b>n=35</b>              |
| Male                                    | 19 (54.3%)               |
| Female                                  | 16 (45.7%)               |
| <b>Age (y), mean (range)</b>            | 48.6 (22-92)             |
| <b>Time to onset (m), mean (range)</b>  | <b>n=34 <sup>b</sup></b> |
|                                         | 4.3 (1-18)               |
| <b>Lesion types</b>                     | <b>n=35</b>              |
| Plaque psoriasis                        | 27 (77.1%)               |
| Pustular psoriasis                      | 3 (8.6%)                 |
| Guttate psoriasis                       | 2 (5.7%)                 |
| Erythrodermic psoriasis                 | 1 (2.9%)                 |
| Reverse psoriasis                       | 1 (2.9%)                 |
| Sebopsoriasis                           | 1 (2.9%)                 |
| <b>Lesion location</b>                  |                          |
| Extremities                             | 27 (77.1%)               |
| Trunk                                   | 13 (37.1%)               |
| Scalp                                   | 11 (31.4%)               |
| Face and neck                           | 4 (11.4%)                |
| Nail                                    | 2 (5.7%)                 |
| <b>Dupilumab discontinuation</b>        | <b>n=33</b>              |
|                                         | 16 (48.5%)               |
| <b>Management</b>                       | <b>n=32</b>              |
| <b>Topical treatment</b>                |                          |
| Topical corticosteroids                 | 27 (84.4%)               |
| Topical vitamin D derivatives           | 6 (18.8%)                |
| Topical calcineurin inhibitors          | 2 (6.3%)                 |
| <b>Phototherapy</b>                     |                          |
| NB-UVB                                  | 2 (6.3%)                 |
| <b>Conventional systemic treatments</b> |                          |
| Oral corticosteroids                    | 4 (12.5%)                |
| Cyclosporine                            | 2 (6.3%)                 |
| Mycophenolate mofetil                   | 1 (3.1%)                 |
| <b>JAK inhibitors</b>                   |                          |
| Delgocitinib ointment                   | 2 (6.3%)                 |
| Upadacitinib                            | 1 (3.1%)                 |
| <b>Outcome</b>                          | <b>n=30</b>              |
| Improvement                             | 28 (93.3%)               |
| Insufficient remission or recurrence    | 2 (6.7%)                 |

<sup>a</sup> Case reports of pediatric patients and flare of pre-existent psoriasis are not summarized in table due to the small sample size, and the detailed information can be found in Table 1.

<sup>b</sup> One case is excluded for a long onset time of 30 months.

y: year, m: month.