

Janus kinase inhibitors enhance the efficacy of dupilumab in refractory atopic dermatitis

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ABSTRACT

Objective: Patients with moderate-to-severe atopic dermatitis (AD) often experience intense pruritus and extensive skin lesions, which markedly impair quality of life. Current treatment options, including biologics and small-molecule agents, may provide limited efficacy and are associated with adverse effects. For patients who respond inadequately to dupilumab, particularly those with insufficient control of pruritus, more effective therapeutic strategies are needed. This study aims to evaluate the efficacy, safety, and clinical value of combining dupilumab with Janus kinase inhibitors (JAKis) in the treatment of refractory AD.

Methods: This retrospective study assessed the efficacy and safety of combination therapy with dupilumab and JAKis in 7 patients with refractory moderate-to-severe AD. Patients received either abrocitinib (100 mg/d) or upadacitinib (15 mg/d) in combination with dupilumab. Disease severity before and after combination therapy was evaluated using the Eczema Area and Severity Index (EASI), Scoring Atopic Dermatitis (SCORAD), Patient-Oriented Eczema Measure (POEM), Dermatology Life Quality Index (DLQI), Itch Numerical Rating Scale (Itch-NRS), and Sleep Disorder Numerical Rating Scale (Sleep-NRS). Adverse events were also recorded.

Results: After 4 weeks of combination therapy, patients with AD who had shown an inadequate response to dupilumab monotherapy exhibited marked improvement in skin lesions. Significant reductions were observed in EASI, SCORAD, POEM, DLQI, Itch-NRS, and Sleep-NRS scores (all $P < 0.05$). All patients achieved an EASI50 (defined as $\geq 50\%$ reduction in EASI score from baseline) criteria. No serious adverse events were reported, except for one case of mild acne.

Conclusion: In patients with AD who show an inadequate response to continued dupilumab treatment, the addition of JAKis can significantly enhance therapeutic efficacy and is generally well tolerated. This combination regimen may represent a promising treatment option for refractory AD.

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KEY WORDS Janus kinase inhibitors; atopic dermatitis; dupilumab; abrocitinib; upadacitinib; combination therapy

Janus 激酶抑制剂改善度普利尤单抗对难治性特应性皮炎的疗效

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[摘要] 目的: 中重度特应性皮炎(atopic dermatitis, AD)患者常伴有剧烈瘙痒和严重皮损, 极大地影响了患者的生活质量。目前临床上常用的治疗方案, 无论是生物制剂还是小分子制剂, 疗效均有限且伴有不良反应。针对度普利尤单抗治疗效果欠佳、瘙痒控制不理想的患者, 亟需探寻更为适宜的治疗策略。本研究旨在探究度普利尤单抗联合 Janus 激酶抑制剂(Janus kinase inhibitors, JAKis)治疗难治性 AD 的疗效、安全性及临床应用价值。方法: 采用回顾性分析, 评估 7 例难治性中重度 AD 患者接受度普利尤单抗联合 JAKis(阿布昔替尼 100 mg/d 或乌帕替尼 15 mg/d)治疗的疗效与安全性。采用湿疹面积及严重程度评分(Eczema Area and Severity Index, EASI)、特应性皮炎严重程度评分(Scoring Atopic Dermatitis, SCORAD)、患者湿疹自我检查评分量表(Patient-Oriented Eczema Measure, POEM)、皮肤病生活质量指数(Dermatology Life Quality Index, DLQI)、瘙痒数字评分量表(Itch Numerical Rating Scale, Itch-NRS)和睡眠障碍数字评分量表(Sleep Disorder Numerical Rating Scale, Sleep-NRS)评估在联合治疗前后患者疾病的严重程度, 并观察不良反应。结果: 联合治疗 4 周后, 对度普利尤单抗单药治疗反应不佳的 AD 患者的皮损明显改善, EASI、SCORAD、POEM、DLQI、Itch-NRS 和 Sleep-NRS 的评分均显著改善(均 $P < 0.05$), 所有患者均达到 EASI50(定义为 EASI 评分较基线降低 $\geq 50\%$)标准。除 1 例轻度痤疮外, 未报告其他严重不良事件。结论: 对度普利尤单抗持续治疗后效果欠佳的 AD 患者, 联用 JAKis 可显著增强其疗效, 且耐受性良好, 可作为难治性 AD 治疗的新选择。

[关键词] Janus 激酶抑制剂; 特应性皮炎; 度普利尤单抗; 阿布昔替尼; 乌帕替尼; 联合治疗

Atopic dermatitis (AD), a chronic, relapsing, inflammatory skin disease, tends to affect individuals with an atopic constitution. Clinically, it is characterized by symptoms including pruritus, erythema, papules, crusting, and lichenification, significantly impacting the quality of life for patients^[1]. Particularly in cases of AD in infants and adolescents, the itching and skin lesions often lead to poor sleep for the patients and their families, affecting work and study during the day^[2]. In severe cases, psychological disorders such as depression and anxiety may occur^[3]. Persistent pruritus in young children may lead to growth retardation if left untreated. The etiology of the disease is not yet clear, with multiple factors including genetics, environment, and immunity playing roles in its development.

For patients diagnosed with AD who experience significant pruritus, the primary treatment objective is the maintenance of effective itch control. For patients with moderate-to-severe AD who do not respond adequately to conventional treatments, the use of

biologics and small-molecule preparations have been shown to be efficacious. Dupilumab, a monoclonal antibody targeting the interleukin (IL)-4R α subunit, can exert its biological effect by specifically blocking IL-4 and IL-13 binding to IL-4R α ^[4]. It can quickly alleviate itching in patients and improve skin lesions. Study^[5] has shown that after treatment with dupilumab, patients' eosinophil counts and immunoglobulin E (IgE) levels can be improved. It is used in the treatment of moderate-to-severe AD in adults and some children older than 6 months with few adverse effects. However, dupilumab demonstrates limited efficacy in treating facial and cervical skin lesions, though in some cases it may induce facial rash^[6].

Janus kinase inhibitors (JAKis), including abrocitinib and upadacitinib, are small-molecule agents used for moderate-to-severe AD that exert therapeutic effects via JAK1 inhibition, which modulates T-cell differentiation and reduces inflammatory cytokine secretion^[7-8]. JAKis can also effectively inhibit IL-6 and

interferon (IFN) γ related signal transduction, but have a depletion effect on natural killer cells^[9-10]. JAKis have a rapid onset of action and can promptly alleviate pruritus and achieve greater improvement in facial and cervical lesions; however, their use is associated with thromboembolic risks, particularly limiting their application in elderly populations^[11-12]. Some patients may even develop infection, secondary acne, liver injury, and reactivation of herpes zoster virus^[13]. Emerging evidence^[14] has reported that transitioning to JAKis after insufficient response to dupilumab monotherapy may be an effective strategy, with the most frequently adopted regimens being abrocitinib 100 mg once daily or upadacitinib 15 mg once daily. In patients with pronounced pruritus and skin lesions who respond poorly to dupilumab, the addition of immunosuppressants or JAKis has been considered a viable therapeutic option. Furthermore, one report^[15] has indicated that combining broad-spectrum JAKis with dupilumab may improve skin lesions with manageable adverse effects. However, such combination therapy is off-label use and has only been studied in small sample cohorts, necessitating further clinical validation.

To provide evidence-based alternative therapeutic options for the management of moderate-to-severe refractory AD, we conducted a retrospective analysis of patients with refractory moderate-to-severe AD treated, who received combination therapy with dupilumab and a Janus kinase inhibitor (JAKi) (either abrocitinib or upadacitinib). The clinical efficacy and potential adverse events of the combination regimen were evaluated, and the clinical outcomes of enrolled patients were retrospectively analyzed.

1 Participants and methods

1.1 Ethics statements

The study protocol was approved by the Medical Ethics Committee of the Third Xiangya Hospital, Central South University (Approval number: 23134).

1.2 Participants

This retrospective analysis included a cohort of 7 patients (all male, mean age: 15.4 $\pm$ 3.0 years, mean disease duration: 12.1 $\pm$ 2.5 years) with moderate-to-severe AD who were treated with dupilumab in combination with JAKis from May 2021 to July 2023 at

the Department of Dermatology, Third Xiangya Hospital, Central South University. Inclusion criteria were: 1) Scoring Atopic Dermatitis (SCORAD) score $\geq$ 25; 2) age $\geq$ 12 years; 3) Investigator's Global Assessment (IGA) score $\geq$ 3 after systemic therapy; 4) complete baseline and 2 follow-up records, and received both JAKi and dupilumab treatment. Exclusion criteria were: 1) Development of severe adverse reactions; 2) development of severe complications or comorbidities. Based on these inclusion and exclusion criteria, 7 cases were ultimately included.

1.3 Treatment strategy

All patients enrolled were initially treated with dupilumab (dupilumab injection dosage: The initial subcutaneous dose was 600 mg, followed by 300 mg subcutaneously every 2 weeks, and then adjusted to 300 mg every 4 weeks). As treatment progressed, the efficacy of monotherapy gradually diminished, leading to inadequate disease control {failure to achieve EASI50 [defined as $\geq$ 50% reduction in Eczema Area and Severity Index (EASI) score from baseline] or Itch-NRS $\geq$ 5}. Subsequently, JAKis (abrocitinib 100 mg once daily or upadacitinib 15 mg once daily) were added for combination therapy.

1.4 Assessment

Patient disease assessment was conducted at 4 time points: Before dupilumab monotherapy, 4 weeks after dupilumab monotherapy, before combination therapy following reduced efficacy of dupilumab monotherapy, and 4 weeks after combination therapy (dupilumab and JAKis). EASI, SCORAD, Patient-Oriented Eczema Measure (POEM), Dermatology Life Quality Index (DLQI), Itch Numerical Rating Scale (Itch-NRS), and Sleep Disorder Numerical Rating Scale (Sleep-NRS) were used for the evaluation of clinical efficacy, and adverse reactions were observed. All patients were administered with moisturizer and tacrolimus ointment throughout the entire treatment course.

1.5 Statistical analysis

Statistical analysis was performed using GraphPad Prism 8 and SPSS 23 software. The results of clinical scores were analyzed by the Wilcoxon test. A *P* value of <0.05 was considered statistically significant.

2 Results

2.1 Efficacy of dupilumab monotherapy in patients with AD after 4 weeks

A total of 7 patients were included in this analysis. Detailed data including age, gender, disease duration, total IgE level, eosinophil count, eosinophil percentage, allergic history, atopic comorbidities, family history, and type of combined JAKi, are summarized in Table 1. For atopic comorbidities, allergic rhinitis (85.7%, 6/7) was more common than asthma (14.3%, 1/7). A total of 57.1% (4/7) of patients had a family history of atopic diseases (Table 1).

Initially, all patients were treated with dupilumab monotherapy. After 4 weeks of treatment, the efficacy was significant, with improvements observed in the scores of EASI, SCORAD, POEM, DLQI, and sleep-NRS (all $P<0.05$, Figure 1). All 7 patients reached EASI50 and 3 patients reached EASI75 (defined as $\geq 75\%$ reduction in EASI score from baseline).

2.2 Duration of dupilumab monotherapy in patients with AD

After receiving dupilumab monotherapy for varying durations, 7 patients with AD experienced a gradual decline in treatment efficacy. When disease control became inadequate, JAKis were added as

combination therapy. The duration of dupilumab monotherapy for these 7 patients was 8, 14, 14, 24, 28, 28, and 48 weeks, respectively.

2.3 Efficacy and safety of JAKis combined with dupilumab in patients with AD

During the combination therapy, 4 patients received abrocitinib as the combined agent, and the remaining 3 received upadacitinib (Table 1). After 4 weeks of combination treatment, the scores of EASI, SCORAD, DLQI, Itch-NRS, and Sleep-NRS were all significantly improved (all $P<0.05$), and all patients achieving EASI50 criteria. Representative skin lesions of one patient at baseline, after 4 weeks of dupilumab, before combination therapy, and after 4 weeks of combination therapy are shown in Figure 2, which demonstrated marked improvement after combination therapy. In order to provide a more comprehensive illustration of the patient's progression, Table 2 presents the scores for one patient at 4 time points during the treatment. For the adverse reactions, only one patient developed secondary acne after JAKi combined therapy. The results showed that the severity of skin lesions and quality of life scores of patients after combination treatment were significantly improved than using dupilumab monotherapy, and the combination treatment demonstrated good safety within 4 weeks.

Table 1 Clinical and demographic characteristics of the AD patients

Cases	Gender	Age/Years	Disease duration/Years	Height/cm	Weight/kg	BMI/(kg·m ⁻²)	IgE/(IU·mL ⁻¹)	EOS/($\times 10^9 \cdot L^{-1}$)
P1	Male	13	13	168	70	24.8	784	1.5
P2	Male	16	12	173	102	34.1	1 510	0.3
P3	Male	15	10	173	76	25.4	2 460	0.2
P4	Male	21	10	172	73	24.7	5 070	0.4
P5	Male	14	13	173	55	18.4	1 3100	0.2
P6	Male	17	17	170	60	20.8	2 713	0.2
P7	Male	12	10	153	51	21.8	2 0420	0.9

Cases	EOS/%	Allergic history	Atopic comorbidities	Family history	Combined JAKi
P1	18.3	Dust mite	Allergic rhinitis, asthma	Asthma of his grandma	Abrocitinib
P2	5.4	—	Allergic rhinitis	—	Abrocitinib
P3	2.9	—	—	Asthma of his father	Upadacitinib
P4	6.4	—	Allergic rhinitis	Allergic rhinitis of his father	Abrocitinib
P5	2.9	—	Allergic rhinitis	—	Upadacitinib
P6	4.9	—	Allergic rhinitis	Allergic rhinitis of his father	Abrocitinib
P7	13.6	Penicillin	Allergic rhinitis	—	Upadacitinib

AD: Atopic dermatitis; BMI: Body mass index; IgE: Immunoglobulin E; EOS: Eosinophils; JAKi: Janus kinase inhibitors.

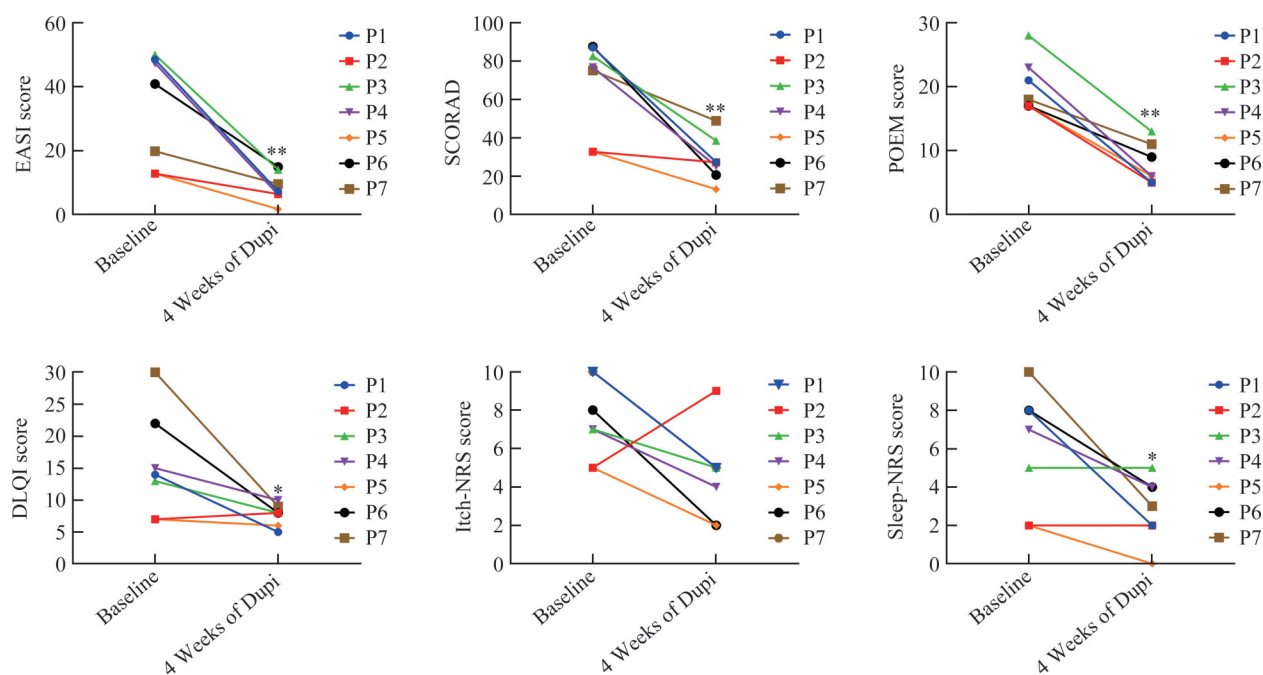


Figure 1 Clinical scores of AD patients before and after 4 weeks of dupilumab monotherapy

Compared to the baseline, * $P<0.05$, ** $P<0.01$. Dupi: Dupilumab; EASI: Eczema Area and Severity Index; SCORAD: Scoring Atopic Dermatitis; POEM: Patient-Oriented Eczema Measure; DLQI: Dermatology Life Quality Index; Itch-NRS: Itch Numerical Rating Scale; Sleep-NRS: Sleep Disorder Numerical Rating Scale.

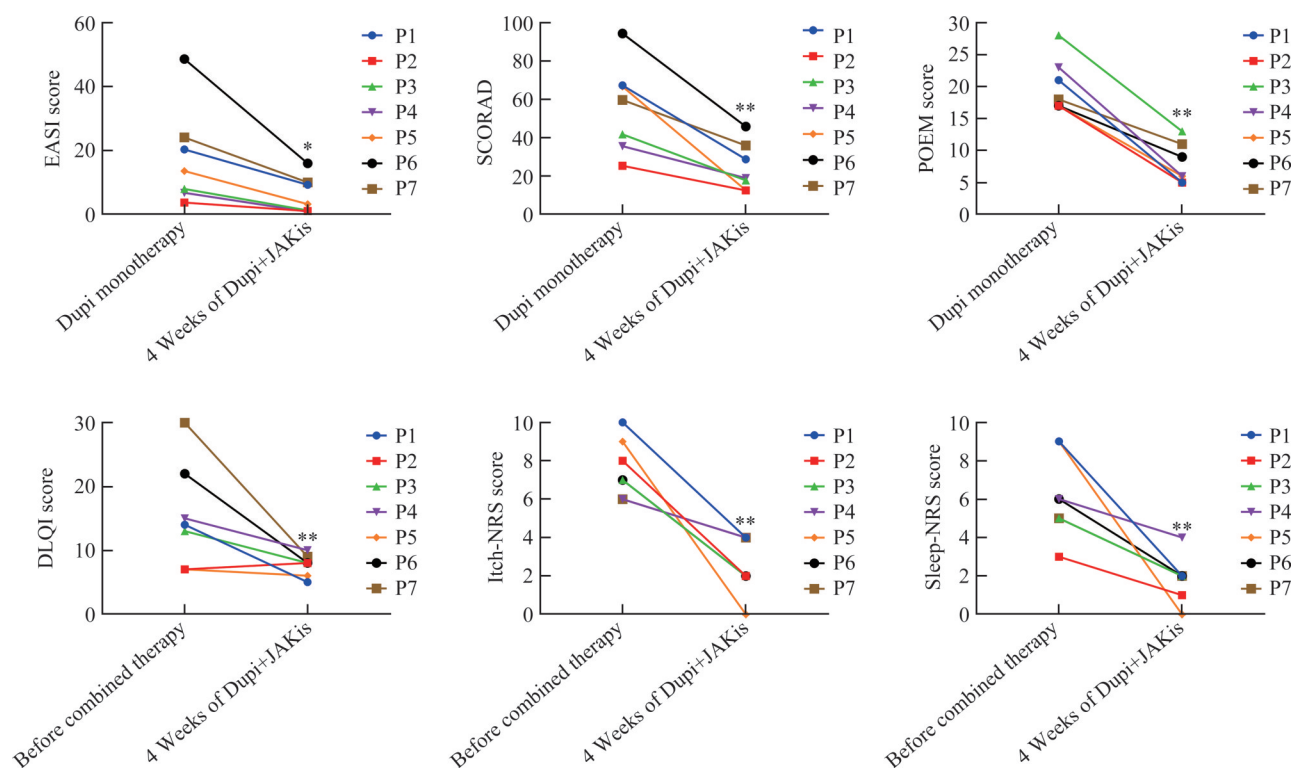


Figure 2 Clinical scores before and after 4 weeks of treatment with JAKis combined with dupilumab in AD patients

Compared to before combination therapy, * $P<0.05$, ** $P<0.01$.

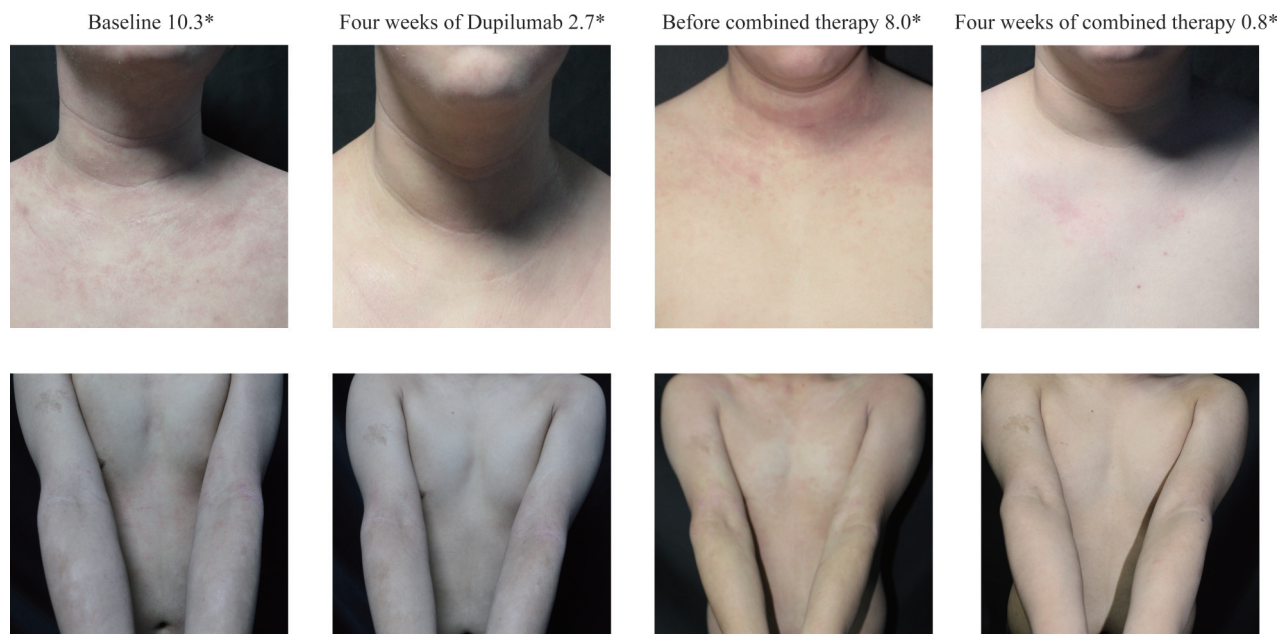


Figure 3 Clinical photographs of P1

*EASI score.

Table 2 Treatment scores of P6 at different time points

Time points	EASI score	SCORAD	POEM score	DLQI score	Itch-NRS score	Sleep-NRS score
Baseline	40.9	87.5	18	22	8	8
Four weeks of dupilumab	14.9	20.7	11	8	2	4
Before combined therapy	48.6	94.6	17	21	7	6
Four weeks of combined therapy	16	45.9	9	8	2	2

3 Discussion

Current therapeutic strategies for refractory AD have evolved to include sequential and combination approaches. While the efficacy of JAKi monotherapy following unsuccessful dupilumab treatment has been systematically investigated, emerging evidence supports 2 distinct therapeutic paradigms. First, combination therapy incorporating dupilumab with tofacitinib as rescue treatment has demonstrated significant clinical efficacy in refractory cases^[16]. Second, well-documented clinical evidence^[17] reveals that a substantial proportion of AD patients achieve marked improvement upon transitioning from JAKis therapy to dupilumab monotherapy, suggesting potential benefits of this therapeutic sequence. However, in the current therapeutic landscape where dupilumab has emerged as the first-line biologic treatment for AD, a critical

knowledge gap persists regarding optimal treatment strategies for suboptimal responders. Specifically, the clinical treatment lacks evidence-based guidelines on systematic combination approaches incorporating JAKis and their associated long-term therapeutic outcomes in this patient population.

In this retrospective study, the 7 enrolled patients demonstrated significant improvements in clinical scores including EASI, SCORAD, POEM, DLQI, and Sleep-NRS after 4 weeks of dupilumab monotherapy, indicating the efficacy of dupilumab for AD. However, the efficacy of dupilumab monotherapy in these refractory AD patients was not sustained. After 8 to 48 weeks of dupilumab monotherapy, satisfactory control of the condition could not be achieved. Consequently, a combination therapy regimen was adopted, incorporating a JAKi abrocitinib or upadacitinib. After 4 weeks of combination therapy, all scores used for

assessment in the study (including EASI, SCORAD, POEM, DLQI, Itch-NRS, and Sleep-NRS) showed significant improvements. The results indicate that combination therapy with JAKis can significantly improve efficacy decline caused by long-term dupilumab monotherapy in short-term. Currently, there are few clinical studies reporting on the combination of dupilumab and JAKis for treating refractory AD. A clinical study^[15] divided 51 patients with moderate-to-severe AD into 2 groups: One group of 29 patients received dupilumab combined with JAKis (tofacitinib or baricitinib), while the other group of 22 patients received dupilumab combined with immunosuppressants (ciclosporin, tripterygium, or corticosteroids) or interval dupilumab monotherapy with dose adjustment. The dupilumab plus JAKi group demonstrated significantly superior efficacy compared to the other group. Throughout the study, 8% of patients experienced mild conjunctivitis that relieved spontaneously^[15]. Our research aligns with the trend.

The potential mechanism underlying the synergistic effect of these 2 treatment methods may be that: Dupilumab exerts its effect by selectively blocking the upstream receptors of IL-4/IL-13 at the extracellular level, whilst JAKis function by inhibiting the downstream kinase of JAK1 at the intracellular level. Through this dual blockade-both intracellular and extracellular-and the bidirectional synergistic action between upstream and downstream pathways, the IL-4/IL-13-JAK/signal transducer and activator of transcription (STAT) core inflammatory axis is rapidly and effectively inhibited, thereby providing effective relief from the symptoms of AD^[7, 18]. When refractory AD patients responded to dupilumab limitedly with facial and cutaneous lesions and uncontrolled pruritus, the combination of JAKis would get short-term significant efficacy with few side effects. Unfortunately, relevant studies^[19-20] have not reported key details such as the optimal duration of JAKi treatment in this combination regimen. In summary, consistent with the aforementioned studies, our study found that dupilumab combined with JAKi can be used in the synergistic treatment of AD patients with poor efficacy of using dupilumab alone.

Nevertheless, this study has several limitations. First, the small sample size leads to gender selection

bias: male patients account for a higher proportion of moderate-to-severe AD cases, especially those with facial and cervical lesions, and this population often has higher expectations for treatment efficacy, but our study only enrolled male patients, and no parallel control group was set. Therefore, the safety and efficacy of this combination therapy require further validation in large-sample randomized controlled studies. In addition, the relatively short follow-up period makes it impossible to exclude low-incidence and long-term adverse events. Clinically, regular monitoring of blood routine, liver, and renal function, as well as the risks of thrombosis and infection, remains essential throughout medication. It is also necessary to strictly standardize medication indications and conduct rigorous screening of high-risk populations. Furthermore, the real-world application of this combination regimen is also limited by medical insurance policies in China: Currently, only one of the 2 agents can be reimbursed per treatment course.

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