Dupilumab With Concomitant JAK Inhibitor—A Novel Strategy For Atopic Dermatitis With Poor Response To Dupilumab

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Research Article

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Abstract

Background: Atopic dermatitis (AD) is a disturbing, relapsing inflammatory skin disease characterized by recurrent eczema foci and intense itching. Due to the effectiveness and safety of Dupilumab, it is considered a savior for AD patients.

Objective: To investigate the efficacy and safety of JAK inhibitors (JAKi) plus Dupilumab therapy in refractory AD patients.

Method: An observational study analyzing the disease control status of refractory AD patients under the treatment of Dupilumab. Data on patients with moderate to severe AD treated with Dupilumab were obtained from the First Affiliated Hospital of Wenzhou Medical University. The clinical effectiveness and safety of Dupilumab combined with JAKi were evaluated and monitored.

Results: Of the 198 patients enrolled, 56 (28.3%) had underreacted to Dupilumab to dupilumab at 16 weeks. Proportion of patients with an improvement from baseline in the Eczema Area and Severity Index (EASI-75) of at least 75% (65.7%;130/198). Five patients eventually discontinued treatment due to adverse reactions. Among uncontrolled patients (n=51) who did not achieve $EASI \leq 7$ or IGA 0/1 during the 16-week study period, 74.5% (38/51) achieved EASI-75 by week 52, including 71.1%(27/38) in combination with JAKi therapy. No significant systemic side effects in the combined JAKi group.

Limitations: Including small sample size, short observation period.

Conclusion: Given the tremendous burden of AD, the demand for new targeted therapies is very high. The combination of JAKi and Dupilumab in AD patients with low response rates may dramatically changing the treatment expectations of patients and doctors.

Key Points

- 1.Dupilumab has proven effective for some patients with uncontrolled atopic dermatitis (AD). What is the next step if Dupilumab fails to treat atopic dermatitis?
- 2.This article addresses combination therapy with Jak inhibitor and Dupilumab may be the promising treatment strategy for the failure of Dupilumab.

Introduction:

Atopic dermatitis (AD) is a chronically disturbing, relapsing inflammatory skin disease.[1] Patients with moderate-to-severe AD generally have extensive skin lesions; often accompanied by intense and persistent itching that interferes with daily activities.[2, 3] The current global estimated prevalence of AD is 15% to 20% in children and 7% to 10% in adults; the prevalence of AD in China has been increased rapidly during the past decade.[4, 5] The pathogenesis of AD is complex, factors such as genetic disorders, immune balance breakdown, skin barrier dysfunction, and skin microbial disorders are

considered to be important links in the occurrence and development of AD.[6-8] Current mainstream treatments, including emollients, topical anti-inflammatory treatments, calcineurin inhibitors, steroids and immunosuppressants; despite these reproved improvements, the need for effective and safe long-term drug therapy has not been met in today's social context.

Emerging topical and systemic therapies primarily target the type 2 immune pathway. Dupilumab, an anti-IL-4R fully human monoclonal antibody, inhibits the biological effects of IL-4 and IL-13, type 2 cytokines.[3, 9-11] Dupilumab is the first biologic therapy approved by the FDA for the treatment of poorly controlled moderate-to-severe AD in children and adults.[5, 12] In multiple clinical trials and practical experience, Dupilumab has been shown to be safe and effective in the treatment of refractory AD.[13-16] However, a small proportion of patients show resistance or uncontrolled disease.[17, 18]

With the increasing application of targeted therapy, JAK inhibitors, a new class of small molecules, have become an important focus of AD treatment research. The Janus Kinase (JAK)/signal transducer and activator of transcription (STAT) pathway is the major regulator of immune function and participates in the downstream signal transduction of inflammatory cytokines.[19, 20] Tofacitinib (CP-690550), a potent and selective JAK inhibitor that preferentially inhibits JAK1 and JAK3, showing promising preliminary data in clinical trials for the treatment of AD and with few data on long-term benefit or safety.[21, 22] Recent studies have also shown that chronic pruritus depends on neuronal JAK1 signaling.[23] The emergence of JAK1 has enabled more selective targeting of only one JAK subtype, thereby inhibiting a narrower range of cytokines.[24] Overall, Janus kinase (JAK) inhibitors are small-molecule inhibitors targeting intracellular signaling pathways, which lack immunogenicity and have good oral bioavailability, which may address some of the limitations of biologics.[23, 25] Little research has been done on what physicians can do to treat AD with insufficient efficacy or worsening of symptoms after subcutaneous administration of Dupilumab. This article aims to focus on assessing the efficacy of JAK inhibitors combination with Dupilumab.

Materials And Methods:

This prospective observational study included all patients with refractory AD treated with Dupilumab. If available, discontinue JAK inhibitors or other systemic immunosuppressive therapy before initiating Dupilumab therapy. Data were obtained from the cohort who started Dupilumab injections at the First Affiliated Hospital of Wenzhou Medical University from August 2020 to October 2021. The Institutional Review Board approved the study and conducted in accordance with research ethics. All patients provided written informed consent. The first dose of Dupilumab was 600 mg followed by 300 mg every other week.

2.1 Patients and outcome measures

Dermatologists assess the control status of AD patients at regular clinic visits. Atopic Dermatitis Control Tool (ADCT) allowing patients and physicians to evaluate the different dimensions of patient-perceived AD control. Disease severity was assessed by Eczema Area and Severity Index (EASI) and the Scoring

Atopic Dermatitis (SCORAD) during the visit. Patient-assessed disease status and treatment effectiveness should be taken into consideration; including the Patient-oriented eczema measurement (POEM), Peak Pruritus Numerical Rating Scale (PP-NRS) and Dermatology Life Quality Index (DLQI). Laboratory tests such as changes in Immunoglobulin E(IgE) can also be used as indicators to observe disease progression.

Currently, there is no accepted definition of treatment failure with Dupilumab. Based on experience and references, treatment failure is concluded that inadequate clinical improvement, failure to relieve impairment or unable to achieve stable long-term disease control, and abnormal skin lesions aggravated or other serious adverse reactions after treatment. In this study, patients who did not reach the indicated disease control indicators ($EASI \leq 7$ and $NRS \leq 4$) at 16 weeks of treatment were considered undertreated; disease exacerbation is defined as a 15% increase in EASI or an increase in NRS from baseline during treatment. In patients with treatment failure, interval adjustment or combination therapy can be used; JAK inhibitors combination or other maintenance systemic therapy such as cyclosporine, methotrexate, and oral corticosteroids are selected. If necessary, other ancillary tests, such as skin biopsies, patch testing, and laboratory analysis, were performed. Observation was continued until the condition is stable and controlled; the mean period of observation was 12 months.

The focus of this study was to demonstrate the efficacy of the Dupilumab combined with JAKi in patients defined as treatment failure(16w). The primary outcome measure was the proportion of patients with an IGA score of 0 or 1 (clear or almost clear) and 75% or greater improvement from baseline in eczema area and severity index (EASI-75) response at 52w. Relative changes over time across treatments (EASI, SCORAD, NRS, POEM, ADCT and DLQI) were analyzed. Adverse events (AEs) were monitored; adhere to continue treatment while common adverse events occur.

3.Statistical Analysis

All statistical analyses were performed with IBM SPSS statistics 26 and GraphPad Prism 8 (GraphPad Software). Statistical significance of changes in different groups before and after treatment were analyzed using Wilcoxon signed-rank test or T test. $P < 0.05$ was statistically significant. All the results were expressed in the form of mean and Standard Deviation (SD) or median and Interquartile Range (IQR), or percentages.

Results:

4.1Population

In total, 198 patients were enrolled (113 males and 85 females), mean age (SD) 40.6(23.0) years (range 12-88 years), with average disease duration was 5.5(5.6) [mean (SD)] years (range 0.2-26 years). At the baseline, 181(91.4%) patients achieved an Investigator's Global Assessment (IGA) score of 3 (moderate) or 4 (severe), 127(64.1%) patients reported at least one concurrent allergic condition and 36(18.2%) had family atopic history. The median total serum IgE in patients (n=163) determined before treatment was

569.7(range 8-2875 KU/m) and ADCT at baseline was 14.1(3.0). All patients received Dupilumab monotherapy (excluding irregular combinations of topical drugs or emollients) after failure of pre-study conventional therapy. In our study cohort, patients (28.3%;56/198) were considered treatment failures at the 16w efficacy assessment after Dupilumab treatment; patients (9.1%;18/198) experienced worsening symptoms and patients (16.7%;33/198) had an insufficient response; none of them stopped Dupilumab treatment. However, patients (2.5%;5/198) had other serious adverse reactions and eventually discontinued treatment of Dupilumab (Table1).

4.2Efficacy of JAK inhibitor combination therapy

To investigate the possible effect of combining JAK inhibitor and biological agents in patients with poor efficacy of Dupilumab monotherapy, we divided patients(n=51) who failed treatment into two groups based on treatment characteristics: 1) Combined treatment with a Dupilumab and JAK inhibitor (mainly tofacitinib 5 mg twice daily) (56.9%;29/51); 2) Dupilumab in combination with other immunosuppressants or adjust dose interval (43.1%;22/51). Among patients(n=51) who did not achieve $EASI \leq 7$ or IGA 0/1 during the 16-week study period, 74.5%(n=38) achieved EASI-75 by week 52, including 71.1%(n=27) combined with JAKi therapy.

In the combined JAKi group, the proportion of patients achieving the IGA 0 or 1 was 93.1% (27/29).

During the observation period, EASI improved significantly from baseline 31.4 ± 27.4 (median $\pm$ IQR) to week 16 (22.4 ± 19.9) and week 52 (2.2 ± 3.4) ($p < 0.001$); the proportion of patients achieving the EASI-75, and EASI-90 was 93.1% (27/29), 69% (20/29) respectively at week 52. The SCORAD values decreased significantly from 78.2 ± 25.0 (Medium $\pm$ IQR) at baseline to 61.6 ± 14.7 at 16 weeks and 10.3 ± 10.9 at 52 weeks ($p < 0.001$). From baseline (7.3 ± 1.7) (Medium $\pm$ IQR) to week 16 (4.0 ± 1.0) and week 52 (2.0 ± 1.0), the change in NRS pruritus was significant, a ≥ 4 point reduction in weekly average pruritus NRS was achieved by 25(86.2%) patients (patients with NRS<4 at baseline were excluded) at week 52. Mean change in POEM from baseline 18.6 ± 4.0 (Mean $\pm$ SD) to 16w 13.3 ± 3.6 and 52 week 5.0 ± 2.3 ($p < 0.01$).

Skin lesions and itching of all patients were improved to a certain extent with the JAKi combination therapy. The patients' quality of life also improved significantly, with mean DLQI from baseline (20.3 ± 6.8) to week 16 (12.5 ± 7.2) and week 52 (4.1 ± 1.7) (Table2).

Group without JAKi combination, the proportion of patients achieving the IGA 0 or 1 (12/22; 54.5%) and the proportion of patients with an $EASI \leq 7$ at 52 weeks (11/22; 50%). There was no significant difference in the reduction of NRS and Serum total IgE from baseline between the two groups. As systemic immunosuppressants have broad immunosuppressive activity and significant side effects, most were reduced or discontinued after 4 months of combination therapy (17/22;77.3%).

We also studied (35.9%;71/198) patients who had been previously used JAK inhibitors. All these patients (mean[SD] age 48.9[5.6] years old) had a long AD history. For these patients, the therapeutic effect fluctuated greatly before combined Dupilumab with JAKi, and the disease progression is not well controlled to meet the desired effect. After the addition of JAKi (tofacitinib) in the setting of dupilumab poorly controlled, the skin condition of patients was well adjusted at 4.2 ± 1.6 weeks; and the percentage

of BSA involvement improved from baseline 52.0 ± 19.0 (median $\pm$ IQR) to 41.3 ± 20.1 at 16 weeks, but significantly improved to 6.0 ± 8.5 after 4 weeks of JAKi combination. No recurrence or serious AEs occurred until 52w. Laboratory monitoring every 2 months.

4.3 Representative case report aggravation (Fig1)

A 64-year-old male patient was diagnosed with severe atopic dermatitis. Conventional treatment is ineffective and disease control is poor, the patient started Dupilumab according to the AD dosing schedule; the skin lesions deteriorated after two weeks of treatment and lasted for 4 weeks, and the itching was not relieved. Punch biopsy was performed on the new lesion and histological diagnosis of spongiform dermatitis to rule out other diseases (Fig2). Adhered to Dupilumab treatment plus tofacitinib 5 mg, twice a day to control disease progression; after 2 weeks, the patient's condition was recovered, followed by alleviated erythema and pruritus, IGA reached 0 at the end point.

4.4 Safety

In all participants, three patients were hospitalized and discontinued treatment due to exacerbation of other systemic diseases (cardiovascular and rheumatic diseases). Pathological results of 2 patients showed psoriasis was converted to adalimumab during treatment. No other significant systemic side effects were observed. Only 4%(n=8) patients developed mild conjunctivitis during treatment and relieved spontaneously, we have not had any cases of keratitis. Patients (13.6%;27/198) experienced recurrence during treatment, with facial redness in eight patients, and one relapsed exacerbation controlled by steroids. At the end of observation, Dupilumab was continued in 61.1%(n=121) patients, partially extending the interval between drug injections. JAKi combination therapy was continued (41.4%;12/29) and the drug dose was reduced to 5 mg per day; (17.2%;5/29) patients selected JAKi single drug to control the disease. Observation time limit still need to be extended, and further safety remains to be seen.

Discussion:

Atopic dermatitis (AD) is a chronically relapsing inflammatory skin disease, which has a great impact on the quality of life of patients. Although traditional treatment is effective, some patients still have a low response rate and a high recurrence rate. In general, biological therapy has been shown to control AD patients who are generally refractory to treatment well. However, there are few studies on insufficient efficacy or worsening of symptoms after subcutaneous injection of Dupilumab. Continuing treatment with Dupilumab were generally better than stopping treatment; treatment-related adverse reactions are few and clinical treatment prospects are broad. The most common AEs with Dupilumab were injection site reactions and conjunctivitis, with few other reports.[5, 13, 15] Many clinical trials support the use of concomitant TCS in the real world to enhance the clinical response to Dupilumab.[26, 27] In our real-life applications, the combination of JAKi and Dupilumab significantly improved the clinical severity and may be a safe treatment for patients with insufficient response to Dupilumab or worsening conditions after treatment. Overall, 65.7% of patients achieved EASI-75 at week 16 of dupilumab treatment, 28.3%

patients considered insufficient response, including patients with worsening skin lesions, unrelieved pruritus, and serious adverse reactions. After combining JAKi or other adjustments, 88.9% of patients achieved EASI-75 at week 52.

With the increasing application of targeted therapy, in parallel to psoriasis, JAK inhibitors are considered to be one of the effective drugs for AD treatment. Compared with conventional drugs such as CsA and azathioprine, JAKi can more specifically inhibit the pathways of AD pathogenesis, resulting in higher efficacy against skin lesions and pruritus with a tolerable safety profile. The most extensive safety data for JAK inhibitors come from balacitinib, ruxotinib, and tofacitinib for the treatment of rheumatoid arthritis and myelofibrosis.[28, 29] JAK inhibitors should be avoided in patients with specific complications such as malignancy, severe renal insufficiency, and cardiovascular disease; and monitoring of patient adverse reactions during use is necessary. During the observation period, some patients who had previously used JAK inhibitors or Dupilumab with poor single-drug efficacy improved significantly within a short period of time after the two drugs in combination. This may indicate that the combined effect is greater than the monotherapy control. In addition, Dupilumab combined with tofacitinib was well tolerated in this study and produced no significant side effects at treatment endpoints. Clinical observed parameters and patient-reported results reflect significant clinical improvement, such as pruritus, pain or discomfort, sleep deprivation, quality of life, and symptoms of anxiety and depression. Therefore, it is speculated that cytokines other than IL-4 and IL-13 may make a more major contribution to the development of AD in Dupilumab non-responders. We hypothesized a combination of Dupilumab and JAK inhibitors treatment in patients with severe AD could achieve inhibition of type 2 system signaling and block a range of cytokine, growth factor, and hormone receptor signaling pathway.[30, 31] Combination therapy could better regulate the immune imbalance, and may ameliorate chronic dermatitis by reducing itching and improving skin barrier function. In most chronic skin lesions, Th1-mediated and Th17-mediated responses are activated, in particular in children and people of Asian descent. Suppression of the Th2 axis by Dupilumab treatment may lead to the activation of other axes such as Th1/Th17, which may explain the aggravation of skin lesions and the slow treatment effect in some cases.[28, 32-36] Further analysis of new skin lesions at different stages of the patient's disease progression is needed.

Conclusions:

Our study shows that sticking to Dupilumab and taking further combination therapy such as a Jak inhibitor (tofacitinib 5 mg twice a day as the initial dose) is a good treatment option for patients and doctors. Determining the next steps for the failure of Dupilumab treatment should be based on different factors, the first is to make a clear diagnosis. For some critically ill patients, combining two drugs may better control the disease progression and achieve satisfactory therapeutic effects. To date, the safety and efficacy of JAKi combination treatments are not clear. Future research will focus on long-term effectiveness and security and creating a model to select the best management solution on the basis of personalization.

Abbreviations:

AD, atopic dermatitis; IGA, Investigator Global Assessment; EASI, Eczema Area and Severity Index; NRS, Peak Pruritus Numerical Rating Scale; SCORAD, SCORing Atopic Dermatitis; ADCT, The Atopic Dermatitis Control Tool; POEM, Patient-Oriented Eczema Measure; DLQI, Dermatology Life Quality Index; IgE, Immunoglobulin E

Declaration:

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Data Availability

The datasets generated during and/or analysed during the current study are available from the corresponding author on reasonable request.

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Tables:

Table1 Demographic and Clinical Characteristics of the Patient Population (N=198)

Characteristic	value
Age, mean (SD), y	40.6(23.0)
Female No. (%)	85(42.9)
BMI, mean (SD)	20.1(3.0)
Duration of AD, mean (SD), y	5.5(5.6)
Family atopic history: No. (%)	36(18.2)
Patients with ≥ 1 concurrent allergic condition, No. (%)	127(64.1)
Patients receiving prior JAK inhibitors for AD, No. (%)	71(35.9)
Previous use of oral immunosuppressive drugs for AD, No. (%)	104(52.5)
Number of Dupilumab injections—mean (SD)	9.4(2.3)
Clinical scores(baseline)	
Patients with IGA score of 3 or 4, No. (%)	181(91.4)
EASI score, mean (SD)	40.5(20.8)
Peak Pruritus NRS score, mean (SD)	7.2(1.6)
SCORAD score, mean (SD)	80.4(14.2)
ADCT score, mean (SD)	14.1(3.0)
POEM score, mean (SD)	19.8(2.9)
DLQI score, mean (SD)	20.5(5.2)
Serum total IgE at baseline, median(range), kU/m	569.75(8-2875)
Proportion of patients with $EASI \leq 7$ at 16w, No. (%)	142(71.7)
Treatment failure of Dupilumab at 16w	
Undertreatment No. (%)	33(16.7)
Aggravation of condition No. (%)	18(9.1)
Serious adverse reactions No (%)	5(2.5)

Abbreviations: *AD*, atopic dermatitis; *IGA*, Investigator Global Assessment; *EASI*, Eczema Area and Severity Index; *NRS*, Peak Pruritus Numerical Rating Scale; *SCORAD*, SCORing Atopic Dermatitis; *ADCT*, The Atopic

Dermatitis Control Tool; *POEM*, Patient-Oriented Eczema Measure; *DLQI*, Dermatology Life Quality Index; IgE, Immunoglobulin E; y, years.

Table2 Insufficient response to Dupilumab (N=51)

Outcomes	Dupilumab combined with JAKi (n=29)	Without JAKi (n=22)
Patients with IGA score 0 or 1 at week 52, No. (%)	27(93.1) ***	12(54.5)
A reduction of IGA score from baseline of at least 2 points, No. (%)	25(86.2) ***	15(68.2)
Patients with EASI-75 score at week 52, No (%)	27(93.1) ***	11(50.0)
Patients with EASI-90 score at week 52, No (%)	20(69.0) ***	6(27.3)
EASI score at baseline, Medium (IQR)	31.4(27.4)	27.3(29.6)
EASI score at week 52, Medium (IQR)	2.2(3.4) ***	9.4(7.5)
SCORAD at baseline, Medium (IQR)	78.2(25.0)	71.9(17.7)
SCORAD at week 52, Medium (IQR)	10.3(10.9) ***	16.8(16.0)
ADCT score at baseline, Mean (SD)	15.1(3.4)	14.5(2.7)
ADCT score at week 52, Mean (SD)	4.1(1.6) **	7.0(2.4)
POEM score at baseline, Mean (SD)	18.6(4.0)	19.5(2.3)
POEM score at week 52, Mean (SD)	5.0(2.3) **	7.9(2.6)
Percent BSA involvement at baseline, Medium (IQR)	52.0(19.0)	54.5(26.0)
Percent BSA involvement at week 52, Medium (IQR)	6.0(8.5) **	16.8(13.0)
NRS score at baseline, Mean (SD)	7.3(1.7)	7.5(1.4)
Proportion of patients with NRS ≤ 2 , No (%)	25(86.2) **	17(77.3)
Total DLQI score at baseline, Mean (SD)	20.3(6.8)	19.9(5.6)
Total DLQI score at week 52, Mean (SD)	4.1(1.7) **	7.0(3.1)
Proportion of patients with DLQI ≤ 5 , No. (%)	24(82.8) ***	8(36.4)
Characteristics of treatment		
Number of Dupilumab injections, Mean (SD)	11.1(2.1)	11(2.3)
Combination treatment duration, Mean (SD), m	5.4(2.3)	4.1(3.6)
Lengthened injection interval, No (%)	13(44.8)	7(31.8)
Maintenance of Dupilumab treatment at final status, No (%)	18(62.1)	14(63.6)

Mean score change in Statistical analyses were performed using GraphPad Prism 8. Quantitative variables are expressed as mean $\pm$ standard deviation and compared with unpaired t tests, or median $\pm$ interquartile range and compared with Wilcoxon tests in case of non-normality. Comparisons of efficacy between baseline and endpoint in all patients, and efficacy comparisons between Dupilumab in combination with JAKi and other treatment groups (**p <0.001, *p <0.01; *p <0.05, ns not significant).

Abbreviations: IGA, Investigator Global Assessment; EASI, Eczema area and severity index; EASI-75,90, EASI score improvement of at least 75%,90%; SCORAD, Scoring atopic dermatitis; ADCT, The Atopic Dermatitis Control Tool; POEM, Patient-oriented eczema measure; BSA, Body surface area; NRS, Numerical rating scale; DLQI, Dermatology life quality index; IgE, Immunoglobulin E; IQR, Interquartile range; m, months.

Figures

Figure 1

Representative case report patient pictures (Aggravated)

(a) A 64-year-old male patient with severe atopic dermatitis before treatment. (b) After Dupilumab treatment initially responded with worsened body surface, enlarged skin lesion area. (c) Then with received Dupilumab combined with JAK inhibitors, this followed by alleviated erythema and pruritus.

Figure 2

Representative case report patient pathology pictures

Pathological pictures of a 64-year-old male at different treatment time points. (a) Acanthus spongiform edema with inflammatory cell infiltration and chronic inflammatory cells can be seen around the dermal blood vessels. (b) Superficial dermal edema and chronic inflammatory cells showing band-like infiltration. (c) Lymphocyte infiltration in the superficial dermis.

Supplementary Files

This is a list of supplementary files associated with this preprint. Click to download.

- [supplementaryfile.xlsx](#)