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ORIGINAL RESEARCH

Predictors for the Efficacy of 4-Week Dupilumab Treatment in Atopic Dermatitis Patients

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Background: Atopic dermatitis (AD) is a common inflammatory disease with heterogeneous clinical features. Certain meaningful phenotypes and clinical features may help better classify AD patients for personalized medicine. To our knowledge, no ideal predictors have been found so far. We aim to investigate clinical predictors for the 4-week efficacy of dupilumab treatment in AD patients in the real world.

Methods: Two hundred and thirty-three AD patients treated with dupilumab were enrolled between June 2020 and December 2023. Patients' information, characteristics, and medical history were collected. They were evaluated at the baseline and 4 weeks after dupilumab treatment and divided into groups according to the Investigator's Global Assessment (IGA) and peak pruritus numerical rating scale (PP-NRS) score. Statistical analyses were used to evaluate potential predictors.

Results: Age increase, late-onset, erythroderma type, and elevation of total serum IgE level were risk factors for poor response after 4-week treatment. Female, atopic personal or family history, and allergic rhinitis were factors for better response. Multivariate logistic regression analysis showed extrinsic AD had a poor reaction than intrinsic AD (OR=4.792,95% CI 1.460–15.732, p=0.010), so did chronic eczema to acute-subacute eczema (OR=2.386,95% CI 1.247–4.566, p=0.009). Trends to decrease the risk were found for allergic rhinitis (OR=0.315,95% CI 0.202–0.967, p=0.001), and atopic family history (OR=0.442,95% CI 0.159–0.622, p=0.041).

Conclusion: Extrinsic AD and chronic lichenoid eczema are risk factors for poor response to 4-week dupilumab treatment, which suggests that AD patients with extrinsic and chronic lichenoid eczema may need more patience for long-term treatment or make other options.

Keywords: Atopic dermatitis, risk factors, biologics

Introduction

Atopic dermatitis (AD) is a common inflammatory disease with heterogeneous clinical features.[1] The complex interplay of genetics, immunology, environmental factors exposure, and skin barrier disorder make AD occur.[2] Because of the heterogeneity, AD has also been divided into subgroups or subtypes based on different features.[3,4] The term phenotype has been used to define different sets of features of AD patients, which can be determined by age, disease severity, disease trajectory, morphological features, medical history, laboratory results [eg serum immunoglobulin E (IgE)], or a certain feature [eg filaggrin (FLG) mutation].[3,5] Meanwhile, although AD is considered a T-helper(Th) 2 inflammation-skewing disease, inflammation cells of Th17, Th22, and Th1 also participate in AD's progress. The molecular characteristics also help to stratify diseases.[6]

According to various features, such as morphological features, disease conditions, genetics, and immunology features, AD can be identified into certain meaningful phenotypes, which may help better classify AD patients for personalized medicine in the future, especially in the era of biologically targeted therapy.[7–11] AD can also be classified

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into extrinsic and intrinsic phenotypes, the IgE level is the key classification factor. The intrinsic subgroup is defined with normal IgE levels without any other atopic personal history.[12] On the contrary, the extrinsic subgroup, always along with the personal atopic background, shows high total and specific IgE levels. Nowadays, more targeted therapeutics, especially the IL-4Rα blockade dupilumab, have been applied to AD treatment.[13,14] Whether any efficacy differences exist among different phenotypes, especially the extrinsic and intrinsic phenotypes still need further research. The four-week efficacy of dupilumab is significant for early therapeutic evaluation and further effectiveness prediction. In this study, we explored clinical predictors for the 4-week efficacy of dupilumab in AD patients.

Methods

Patients and Study Design

This study enrolled two hundred and fifty-three moderate-to-severe AD patients treated with dupilumab in Henan Provincial People's Hospital between June 2020 and December 2023. Experienced dermatologists diagnosed AD patients according to the Hanifin & Rajka criteria.[15,16] Baseline patients' characteristics, information, and medical history were collected. They were treated with 600mg of dupilumab loading dose and 300mg every other week. Investigator's Global Assessment (IGA) and peak pruritus numerical rating scale (PP-NRS)[17] were evaluated at the baseline and 4 weeks after dupilumab treatment. The target of the 4-week dupilumab treatment was the IGA score to decrease to 0/1 or decrease by more than 2 points or the PP-NRS score to decrease by more than 4 points or drop to less than 3 points. This study has been approved by the Ethics Committee of Henan Provincial People's Hospital (Approval no.2021–161) and Beijing Friendship Hospital (Approval no.2020-P2-296-01), and informed consent was also obtained from all the patients. This study complies with the principles of the Declaration of Helsinki.

Statistical Analyses

Continuous variables were reported as means and standard deviation (SD) or median and interquartile, categorical variables were expressed as frequencies and percentages. Independent sample *t*-test was used to compare continuous variables between groups; the Chi-square test and Fisher's exact were used to compare categorical variables between groups. Univariate logistic regression analysis was performed and factors with $p<0.1$ were included in the multivariate logistic regression analysis, which can be used to evaluate the potential relationship between certain factors and the efficacy of dupilumab. The missing value was deleted or imputed with multiple imputations. $p<0.05$ suggested statistical significance. All the statistical analysis used SPSS software (version 21.0, IBM, Armonk, N.Y., USA).

Results

Demographics

A total of 253 patients were enrolled, and 233 patients satisfied the 4-week dupilumab treatment and were included in the 4-week evaluation. There were 142 men and 91 women, the average age of these patients was 41.67±23.28 years (range, 3–92). The detailed baseline demographics and clinical characteristics of AD patients can be seen in Table 1. Demographics included sex, age, onset of age, different lesion expressions involved such as acute/subacute eczema or chronic lichenoid eczema, generalized or localized, different positions involved, flexion involved, different phenotypes such as intrinsic or extrinsic, prurigo type, erythrodermic type, whether have atopic personal or family history, complicating diseases such as mental disease, urticaria. The laboratory examination indexes eosinophils (EOS), EOS %, basophils (BASO), and serum total IgE were also included in this study.

Efficacy and Potential Predictors

One hundred and fifty-three patients reached the target after 4 weeks of dupilumab treatment, and 80 patients did not achieve the aim of the target. The comparison between clinical features and 4-week efficacy showed that age increase, erythrodermic type, and serum total IgE elevation were risk factors for reaching the treatment target. On the contrary, female, atopic personal history, concomitant allergic rhinitis, and atopic family history were protective factors for treating the target (Table 1).

Table 1 The Baseline Demographics, Clinical Characteristics, and 4-week Efficacy of Dupilumab in AD Patients

Variable	Patients (n=233)	4-Week Efficacy		t/χ^2	*p*
		Treat-to-Target	Non-Treat-to-Target		
Sex, n(%)					
Male	142(60.9%)	85(36.5%)	57(24.5%)	5.436	0.020*
Female	91(39.1%)	68(29.2%)	23(9.9%)		
Age, mean (SD)		38.9(22.7)	46.9(23.6)	−2.53	0.012*
Age of onset, n(%)					
≤6	45(19.3%)	32(13.7%)	13(5.6%)	6.867	0.076
6–18	35(15.0%)	28(12.0%)	7(3.0%)		
>18-70	129(55.4%)	81(34.8%)	48(3.4%)		
≥70	24(10.3%)	12(5.2%)	12(5.2%)		
Medication time, n(%)					
4 week-16 week	106(45.5%)	70(30.0%)	36(15.5%)	0.231	0.891
16 week-1 year	95(40.8%)	61(26.2%)	34(14.6%)		
≥ 1 year	32(13.7%)	22(9.4%)	10(4.3%)		
Phenotypes, n(%)					
Acute/subacute eczema	136(58.4%)	96(41.2%)	40(17.2%)	3.512	0.061
Chronic eczema	97(41.6%)	57(24.5%)	40(17.2%)		
Intrinsic	26(11.1%)	22(9.4%)	4(1.7%)	3.849	0.050
Extrinsic	191(82.0%)	125(53.6%)	66(28.3%)		
Prurigo type	44(18.9%)	25(10.7%)	19(8.2%)	1.883	0.217
Erythrodermic type	8(3.5%)	2(0.9%)	6(2.6%)	4.352	0.021*
Lesion involved, n(%)					
Head and neck	160(68.7%)	105(45.1%)	55(23.6%)	0.000	0.985
Trunk and limbs	227(97.4%)	147(63.1%)	80(34.3%)		0.097
Hand and feet	58(24.9%)	34(14.6%)	24(10.3%)	1.70	0.192
Flexion involved	114(48.9%)	81(34.8%)	33(14.2%)	2.873	0.090
Generalized	209(89.7%)	133(57.1%)	76(32.6%)	3.705	0.054
Localized	24(10.3%)	20(8.6%)	4(1.7%)		
Atopic personal history, n(%)	114(48.9%)	84(36.1%)	30(12.9%)	6.366	0.013*
Allergic rhinitis	102(43.8%)	80(34.3%)	22(9.4%)	10.114	<0.001***
Asthma	27(11.6%)	19(8.2%)	8(3.4%)	0.300	0.670
Allergic conjunctivitis	14(6.0%)	11(4.7%)	3(1.3%)	0.576	0.448
Atopic family history, n(%)	58(24.9%)	45(19.3%)	13(5.6%)	4.867	0.037*
Complicating disease, n(%)					
Mental disease	14(6.0%)	9(3.9%)	5(2.1%)	0	1.000
Urticaria	15(6.4%)	12(5.2%)	3(1.3%)	0.861	0.273
EOS	197(84.5%)	0.57±0.61	0.74±0.92	1.417	0.160
EOS%	198(85.0%)	7.58±7.08	9.21±8.24	1.391	0.167
BASO	195(83.7%)	0.04±0.03	0.05±0.06	1.348	0.179
Total IgE, n(%)					
Normal	51(26.4%)	41(80.4%)	10(19.6%)	7.253	0.027*
Evalated	142(73.6%)				
100–2500	115(59.6%)	70(36.3%)	45(23.3%)		
>2500	27(14.0%)	15(7.8%)	12(6.2%)		

Notes: *: $p< 0.05$, ***: $p< 0.001$.
Abbreviations: EOS, eosinophils; BASO, basophiles.

The univariate logistic regression analysis was performed on the relationship between relevant clinical features and the 4-week efficacy of dupilumab in AD patients. The statistical analyses indicated that there were significant differences between treatment efficacy and clinical features including sex (OR=0.504,95% CI 0.282–0.901, p=0.021), age

(OR=1.015,95% CI 1.003–1.027, p=0.013), age of onset (OR=1.383,95% CI 1.013–1.887, p=0.041), erythroderma type (OR=6.122,95% CI 1.206–31.066, p=0.029), atopic personal history (OR=0.493,95% CI 0.283–0.857, p=0.012), concomitant allergic rhinitis (OR=0.346,95% CI 0.193–0.621, p=0.000), atopic family history (OR=0.466,95% CI 0.234–0.927, p=0.030), serum total IgE (OR=1.864,95% CI 1.137–3.057, p=0.014), which meant that factors of age increase, late-onset, erythroderma type, and serum total IgE were not conducive to reach the target of 4-week dupilumab treatment. On the contrary, female, atopic personal history, atopic family history, and concomitant allergic rhinitis were protective factors for achieving the target (Table 2).

Table 2 Result of Univariate Logistic Regression Analysis on the Relationship Between Relevant Clinical Features and the 4-week Efficacy of Dupilumab in AD Patients

Variable	B	S.E.	Wald	P	OR	OR 95% CI	
Sex							
Male							
Female	−0.684	0.296	5.354	0.021*	0.504	0.282	0.901
Age	0.015	0.006	6.134	0.013*	1.015	1.003	1.027
Age of onset							
≤6							
6–18							
>18-70							
≥70	0.324	0.159	4.176	0.041*	1.383	1.013	1.887
Medication time							
4 weeks-16 weeks							
16 weeks-1 year							
≥1 year	−0.023	0.197	0.014	0.907	0.977	0.664	1.438
Phenotypes							
Acute/subacute eczema							
Chronic eczema	0.521	0.279	3.486	0.062	1.684	0.974	2.911
Intrinsic							
Extrinsic	1.066	0.564	0.567	0.059	2.904	0.961	8.779
Prurigo type	0.467	0.342	1.864	0.172	1.595	0.816	3.116
Erythrodermic type	1.812	0.829	4.780	0.029*	6.122	1.206	31.066
Lesion involved							
Head and neck	20.594	>1000	0.000	0.999	>1000	0.000	
Trunk and limbs	0.405	0.312	1.689	0.194	1.500	0.814	2.765
Hand and foot	0.405	0.312	1.689	0.194	1.500	0.814	2.765
Generalized							
Localized	−1.050	0.566	3.437	0.064	0.350	0.115	1.062
Flexion involved	0.471	0.279	2.856	0.091	1.602	0.927	2.768
Atopic personal history	−0.708	0.282	6.279	0.012*	0.493	0.283	0.857
Allergic rhinitis	−1.061	0.298	12.663	0.000*	0.346	0.193	0.621
Asthma	−0.244	0.446	0.299	0.585	0.784	0.327	1.878
Allergic conjunctivitis	−0.687	0.667	1.063	0.302	0.503	0.136	1.857
Atopic family history	−0.764	0.351	4.736	0.030*	0.466	0.234	0.927
Complicating disease							
Mental disease	0.065	0.576	0.013	0.911	1.067	0.345	3.296
Urticaria	−0.781	0.661	1.398	0.237	0.458	0.125	1.672
EOS	0.312	0.203	2.354	0.125	1.366	0.917	2.034
EOS%	0.028	0.019	2.067	0.151	1.028	0.990	1.068
BASO	4.702	3.830	1.507	0.220	110.119	0.060	>1000

(*Continued*)

Table 2 (Continued).

Variable	B	S.E.	Wald	*P*	*OR*	*OR* 95% CI	
Total IgE							
Normal							
Elevated							
100–2500							
>2500	0.623	0.252	6.087	0.014	1.864	1.137	3.057

Note: *: $p< 0.05$.
Abbreviations: EOS, eosinophils; BASO, basophiles.

Table 3 Result of Multivariate Logistic Regression Analysis on the Relationship Between Relevant Clinical Features and the 4-week Efficacy of Dupilumab in AD Patients

Variable	B	S.E.	Wald	*P*	OR	OR 95% CI	
Intrinsic/extrinsic	1.567	0.607	6.674	0.010	4.792	1.460	15.732
Acute/chronic eczema	0.869	0.331	6.894	0.009	2.386	1.247	4.566
Allergic rhinitis	1.156	0.348	4.178	0.001	0.315	0.202	0.967
Atopic family history	0.816	0.399	11.064	0.041	0.442	0.159	0.622
Constant	2.661	0.754	12.449	0.000	0.070		

Factors with $p<0.1$ in the univariate logistic regression analysis were included in the multivariate logistic regression analysis. The results of multivariate logistic regression analysis showed that factors of intrinsic/extrinsic phenotype, acute-subacute/chronic lesion types, concomitant allergic rhinitis, and atopic family history might affect the efficacy of 4-week dupilumab treatment and existed significant statistical differences (Table 3). Compared with intrinsic, patients with extrinsic phenotype more easily failed to achieve the goal after 4-week dupilumab treatment (OR=4.792,95% CI 1.460–15.732, p=0.010), and so did patients with chronic lichenoid lesions. When compared with acute-subacute patients (OR=2.386,95% CI 1.247–4.566, p=0.009). Trends to decrease the risk of not reaching the target were found for concomitant allergic rhinitis (OR=0.315,95% CI 0.202–0.967, p=0.001), and atopic family history (OR=0.442,95% CI 0.159–0.622, p=0.041).

Discussion

Dupilumab has been approved and used in AD patients for several years. Although some of the real-world research about the efficacy of dupilumab showed better efficacy than the research of SOLO1 and SOLO2,[18–20] many patients still failed to reach the treatment target. Studies on the potential biomarkers or predictors from patients' skin, serum, or other sources had been explored,[21–26] however, no ideal biomarkers had been found and could be used to predict the efficacy of dupilumab.[27] Since biomarkers may not be good enough to predict the treatment efficacy, clinical characteristics might provide hints for us to guide the treatment, which were easy to acquire and evaluate without pain. Four weeks was an important time point for early evaluation and might provide some clues for the effect of 16-week dupilumab treatment. Some patients may decide whether to continue this treatment according to the early treatment effect. We aimed to explore the early potential clinical predictors of the treatment response of AD patients, which might help predict the efficacy of dupilumab and guide future personalized treatment.

Our study found significant differences between clinical characteristics and the 4-week dupilumab treatment effect. Age increase, erythrodermic type, and serum total IgE elevation were risk factors for reaching the treatment target. On the contrary, female, atopic personal history, concomitant allergic rhinitis, and atopic family history were protective factors for reaching the target. The univariate logistic analysis showed almost the same results, except for one more risk factor of late-onset. Previous studies about the factors associated with dupilumab response reported that female sex,

young age, absence of allergic rhinitis, low body mass index, and low blood eosinophil count were associated with a favorable response to dupilumab in patients with AD.[28] Male gender is a negative predictor for maintenance of response to treatment with dupilumab.[29,30] Our study was almost consistent with the reported literature except for the concomitant of allergic rhinitis and blood eosinophil count. Given that the assessment time point in our study is 4 weeks, as opposed to the 12–16 week period commonly reported in the literature, discrepancies may arise.

For the intrinsic and extrinsic phenotypes of AD patients, we found that although the intrinsic AD patients did not have the two protective factors of atopic personal history and atopic family history, patients with intrinsic phenotypes also showed good effects of dupilumab in the multivariate logistic analysis, which was in concordance with the previous literature.[31] Conversely, some patients with extrinsic phenotypes may show poor responses to dupilumab due to various contributing factors. Extrinsic AD patients always show high serum IgE levels, which was a risk factor. At the same time, atopic personal history included not only the protection factor of allergic rhinitis but also asthma, allergic conjunctivitis, and other allergic conditions. On the other side, the Th2 cells mainly participated in the progress of the inflammation; however, other mixed inflammations of Th1, Th17, and Th22 also took part in the progress of the disease, especially in patients with features of chronic, old, late-onset, which expressed similar molecular features.[32,33] The immune imbalance might also affect the treatment effect.

This study also has some limitations. Firstly, the number of AD patients involved was limited. More patients and data from multicenter studies will be explored in the future for better prediction effects. Second, since it was a real-world study, potential bias might be unavoidable. In addition, this was a short-term study about the efficacy of dupilumab, long-term efficacy needed further follow-up and evaluation.

Conclusion

In summary, extrinsic AD and chronic lichenoid eczema are risk factors for poor response to 4-week dupilumab treatment. It suggests that AD patients with extrinsic and chronic lichenoid eczema may need more patience for long-term treatment or make other options. Concomitant allergic rhinitis and atopic family history are positive predictors of dupilumab in AD patients. These predictors for the efficacy of 4-week dupilumab treatment might help clinicians better use dupilumab and guide future personalized treatment.

Disclosure

The authors report no conflicts of interest in this work.

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