Hindawi
Dermatologic Therapy
Volume 2023, Article ID 5626410, 6 pages
https://doi.org/10.1155/2023/5626410

Research Article

Dupilumab Improves Clinical Scores in Pediatric Patients Aged 2 to <18 Years with Uncontrolled Atopic Dermatitis: A Single-Center, Real-World Study

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Received 31 October 2022; Revised 25 March 2023; Accepted 30 March 2023; Published 17 April 2023

Academic Editor: Imran Majid

Dupilumab is the first biologic agent approved for treatment of moderate to severe atopic dermatitis (AD). Phase 3 clinical trials have shown the efficacy and safety in AD children. However, real-world evidence is still scarce. Thirty-nine pediatric patients with uncontrolled AD who regularly received dupilumab were included in a single-center retrospective study. Eight patients (20.5%) were aged 2 to <6 years, fifteen (38.5%) were 6 to <12 years, and sixteen were 12 to <18 years. Changes in clinical AD scores (EASI, SCORAD, P-NRS, CDLQI, and POEM) at baseline, week 4 (W4), W10, and W16, as well as safety data were collected. At W16, the average EASI values dropped from 29.0 ± 16.2 to 5.1 ± 4.7, and 22 patients (73.3%) achieved 75% improvement in EASI. 16 patients (53.3%) achieved 75% improvement in SCORAD. Significant reduction was also observed in the changes of P-NRS, CDLQI, and POEM values. Notably, the change of clinical scores was similar among three age subgroups. At W16, the mean percent decreases in EASI for 2 to <6 years, 6 to <12 years, and 12 to <18 years, and subgroups were 67.3%, 78.5%, and 83.9%, respectively. A total of three cases of adverse effects were recorded, with conjunctivitis seen in two >6-year-old patients and the injection site reaction in one <6-year-old child. Dupilumab exhibited favorable efficacy and safety profile, including the 2 to <6 years old subgroup.

1. Introduction

Atopic dermatitis (AD), characterized by chronic pruritus and eczematous lesions, is one of the most common inflammatory skin diseases in infants and children [1]. Globally, the lifetime prevalence of AD varies between 0.2% and 25%, representing a substantial health and socioeconomic burden [2]. The skin disorders of moderate to severe AD in children have a greater impact on the quality of life such as reduced school performance, poor sleep quality, and symptoms of depression and anxiety [3]. Moreover, recent studies suggest children with more severe disease were more likely to have disease persist in adolescence and adulthood [4, 5]. Thus, there is a significant unmet need for treatment that can lead to rapid disease improvement in children with AD.

The pharmacologic management of pediatric patients with uncontrolled AD is challenging, for the safety consideration, as well as for the impact of family members' quality of life. Topical therapies relying on emollients, topical corticosteroids (TCS), and calcineurin inhibitors (TCI) have limited impact in relieving effects on controlling acute disease flare and long-term progression. Phototherapy such as narrow-band UVB (NB UVB) is not recommended for children given its carcinogenic potential [6]. Moreover, the effectiveness of phototherapy is strictly linked to the compliance of the patient's family members. Short-term systemic corticosteroids and immunosuppressants (cyclosporine, methotrexate, or azathioprine) are established [7] but require continuous monitoring for systemic adverse events (AEs), including procarcinogenic effects, hepatic and renal toxicity, and others [8].

Dupilumab, a fully human monoclonal antibody that blocks the interleukin-4 receptor subunit α (IL-4Rα), is the first biologic approved worldwide for children and adolescents with moderate to severe AD. Recently, the US Food and Drug Administration approved dupilumab for the treatment of children aged 6 months to <6 years following the inspiring outcomes of phase 2 and 3 trial (Liberty AD PRESCHOOL) published in 2021 and 2022 [9, 10]. However, real-world data on the effectiveness and safety of dupilumab in the pediatric AD population, especially in those under 6 years old, are scant.

The present retrospective study aimed to evaluate the effectiveness and safety of dupilumab from baseline to W16 of treatment in AD patients aged 2 to <18 years in a real-world setting. Typically, the clinical data in 2 to <6 years preschool patients were compared with the older age groups.

2. Methods

We conducted a retrospective observational study from March 2021 to September 2022 at Union Hospital, Tongji Medical College, Huazhong University of Science and Technology, as approved by the medical ethics committee. The diagnosis of AD was performed based on the Hanifin and Rajka criteria by a dermatologist who possessed vice professor title or above. Pediatric AD patients aged under 18 years with uncontrolled disease condition and treated with dupilumab for at least 16 weeks were included. A total of 39 pediatric AD patients met the criteria. 15 patients were administered an initial dose of 600 mg, and 8 patients were 300 mg, following 300 mg dose every 4 weeks; other 16 patients who were administered an initial dose of 600 mg received regimen of 300 mg every 2 weeks. During the dupilumab treatment, 13 patients were administrated with only topical corticosteroids (TCS) as topical medication, 6 patients were administrated with only topical calcineurin inhibitors (TCI), and 10 patients were administrated with the TCS and TCI (Supplementary table 1).

Patients were further divided into 2 to <6 years, 6 to <12 years, and 12 to <18 years old subgroups for the following evaluation. Their demographics variables, comorbidities, dupilumab dosing, prior, and concomitant treatments for AD, adverse events (AEs), Eczema Area and Severity Index (EASI), the SCORing AD (SCORAD), Pruritus Numerical Rating Scale (P-NRS), Children's Dermatology Life Quality Index (CDLQI) score, and Patient-Oriented Eczema Measure (POEM) at baseline and after week 4 (W4), W10 and W16 of dupilumab therapy were collected and confirmed by reviewing electronic medical records and contacting guardians. Of them, three patients missed score assessments at W4; seven patients missed at W10; nine patients missed at W16. Laboratory tests for total serum immunoglobulin *E* (IgE) and eosinophil count were also collected.

The statistical analysis was performed using SPSS version 15 (SPSS Inc., Chicago, IL, USA) and GraphPad Prism version 6.0 (GraphPad Software Inc., San Diego, CA, USA) and using multivariate regression and linear mixed-effect models. All statistical tests were two-tailed, and $P < 0.05$ was considered statistically significant.

3. Results

The baseline demographics and disease information are detailed in Table 1. The mean ± SD age at AD onset was 3.8 ± 4.1 years (range, <1 month to 16 years), and the mean ± SD duration of AD symptoms was 6.2 ± 3.9 years. The mean age at dupilumab treatment initiation was 9.9 ± 2.9 years. The cohort had a high prevalence of atopy at baseline; 30/39 of patients (76.9%) had one or more atopic comorbidity before starting dupilumab treatment. Allergic rhinitis was the most frequent atopic comorbidities (24/39; 61.3%), followed by environmental allergies (17/39; 33.7%) and food allergies (13/39, 33.3%). In analyzing patient family medical histories, AD prevalence in the first-degree relatives was seen in 11 children (28.2%). In regards to the previous treatments, 34 and 30 children had been treated with TCS and TCI; 11 and 7 had been prescribed cyclosporine A and systemic corticosteroids; 3 had previously traditional Chinese medicine. Increases in eosinophils and total IgE were detected in 66.7% and 61.5% of children.

For the 2 to <6 years subgroup, 3 girls and 5 boys were enrolled, who were all treated by dupilumab, fully considering the guardian' intent. Their mean age was 4.25 years, and the average length of disease duration was 2.8 years. The included preschool AD patients had body mass index (BMI) between 14.1 and 16.8, and only one 3-year-old boy weighted below 15 kg at treatment. 4/8 (50.0%) of them displayed elevations in eosinophils and total IgE, similar to the whole cohort (Supplementary table 2).

3.1. Dupilumab Effectiveness. The mean EASI score for AD children aged 2 to <18 years was 29.0 ± 16.2 at baseline and significantly decreased to 16.7 ± 9.6 ($p < 0.0001$) and 5.1 ± 4.7 ($p < 0.0001$) after 4 and 16 weeks, respectively. A total of 27 (90.0%) and 22 (73.3%) of children reached 50% improvement in EASI (EASI-50) and 75% improvement in EASI (EASI-75) at W16. The mean SCORAD score decreased from 68.1 ± 18.5 at baseline to 16.7 ± 11.6 at W16 ($p < 0.0001$). At W16, 29 out of 30 (96.7%) children achieved 50% improvement in SCORAD (SCORAD-50) and 53.3% achieved 75% improvement in SCORAD (SCORAD-75). The pruritus symptom assessed by P-NRS was markedly improved, as shown by the scores numerically dropping from 7.9 ± 1.7 at baseline to 1.9 ± 1.4 at W16 ($p < 0.0001$). The 16-week dupilumab treatment also resulted in a marked improvement of CDLQI and POEM. A baseline value of 14.2 ± 5.8 versus 2.8 ± 3.3 at W16 ($p < 0.0001$) was observed for CDLQI, as well as an initial value of 19.6 ± 5.6 versus 3.4 ± 2.7 at W16 ($p < 0.0001$) for POEM (Table 2). Eosinophil levels decreased significantly from 797.5 ± 450.0 mm^3 at baseline to 300.0 ± 280.2 mm^3 with dupilumab therapy for 16 weeks ($P < 0.01$, $n = 8$). There was also an impressive declining trend of total IgE levels from 1138.8 ± 1248.8 IU/mL to 232.3 ± 222.4 IU/mL ($P = 0.06$, $n = 7$) (Supplementary figure 1). Moreover, in a multivariate regression model, we found that combination strategy with dupilumab and the age starting dupilumab were positively correlated with EASI improvement ($P < 0.05$) (Supplementary table 3). And no

significant associations were found between clinical improvement and demographics such as age at atopic dermatitis onset, sex, history of atopic comorbidities, and eosinophils, and total IgE levels increase.

Impressively, we observed a similar improvement trend among the three age groups in aspects of all clinical AD score parameters during the 16-week treatment period (Figure 1, supplementary table 4). In the ≥2 to <6 years group, the baseline EASI score gradually decreased for 78.5% ± 10.7% by W16. Similarly, a total reduction of 80.3% ± 7.8% relative to the baseline EASI score was observed for the ≥6 to <12 years group, and a reduction of 83.9% ± 14.3% for the ≥12 to <18 years subgroup. At W16, the mean percent decreases in SCORAD for the ≥2 to <6 years group were 76.7% ± 10.1%, in correspondence to 74.3% ± 10.3% and 75.9% ± 17.7% for the other two subgroups. Besides, the ≥2 to <6 years group numerically reached a marked decrease in mean P-NRS (Δ6.0), CDLQI (Δ15.5), and POEM (Δ11.2) scores at W16, in line with the older AD groups.

3.2. Dupilumab Safety. Only 3 out of 39 (7.7%) patients experienced AEs during the 16-week treatment (Table 3). None discontinued dupilumab owing to these side effects. Conjunctivitis was seen in an 11-year-old and a 17-year-old patient, but both achieved symptom resolution with artificial tears (5.1%). One (2.7%) child aged 4 had an injection site reaction after the second injection but resolved soon without extra intervention. No serious treatment-emergent AEs, such as systemic anaphylaxis, serum sickness-like reactions, or life-threatening infections, were reported. Of note, during the follow-up phone calls (1 month to 19 months after the W16 injection), none of the children reported further emergent AEs.

Table 1: Demographic and clinical baseline characteristics of pediatric patients ($n = 39$).

Variable	Value
Sex, male, *n* (%)	21 (53.8)
Body mass index, mean ± SD	17.3 (2.9)
Age at atopic dermatitis onset, *y* (mean ± SD)	3.8 (4.1)
Duration of atopic dermatitis, *y* (mean ± SD)	6.2 (3.9)
Age at dupilumab start, *y* (mean ± SD)	9.9 (4.5)
Age at dupilumab start, *y* (*n* (%))	
3–5	8 (20.5)
6–12	15 (38.5)
13–17	16 (41.0)
History of atopic conditions, *n* (%)	
Patients with ≥1 atopic comorbidity	30 (76.9)
Asthma	4 (10.3)
Allergic rhinitis	24 (61.3)
Food allergies	13 (33.3)
Environmental allergies	17 (43.6)
Allergic rhinoconjunctivitis	2 (5.1)
Drug allergy	2 (5.1)
Family history, *n* (%)	
Atopic condition, first-degree relative	11 (28.2)
Atopic condition, second-degree relative	1 (2.6)
Previous systemic treatments, *n* (%)	
Systemic corticosteroids	7 (17.9)
Cyclosporine	11 (28.2)
Omalizumab	1 (2.6)
Traditional Chinese medicine	3 (7.7)
Previous topical treatments, *n* (%)	
Emollients	39 (100)
Topical corticosteroids	34 (87.2)
Topical calcineurin inhibitors	30 (76.9)
Laboratory tests at baseline, *n* (%)	
Eosinophils increase	26 (66.7)
Elevated total serum immunoglobulin E levels	24 (61.5)

4. Discussion

To the best of our knowledge, this is the first real-world study on dupilumab treatment for AD children aged 2 to <18 years in the Chinese population, divided into three age groups. Additionally, we were the first to supplement the real-world data at W16 in China. Since AD control is a broad concept that requires a multidimensional evaluation system, we included five AD clinical scoring scales (EASI, SCORAD, P-NRS, CDQI, and POEM.) to comprehensively assess their disease burden. Moreover, in this real-world study, most pediatric patients were treated based on the clinicians' personal experience before dupilumab was approved in China for children aged under 12 years; thus, it provides an improved understanding of how children respond to this biologic in regards to the efficacy and adverse effects.

We found that dupilumab effectively controlled AD and improved the quality of life in AD children, regardless of their age during the 16-week treatment period. A significant decrease of mean EASI was already seen at W4, changing from 29.0 ± 16.2 at baseline to 5.1 ± 4.7, which was the same for all the other AD scores, reflecting an overall and rapid therapeutic effect with the biologic treatment. At W16, most children experience a further clinical improvement with 73.3% achieving EASI-75. Notably, the SCORAD, NRS, CDLQI, and POEM were also significantly improved, which reflects the dupiluamb benefit in aspects of patient-oriented disease burden, including daily pruritus, sleep disorder, school performance, and others. Different from other studies which showed no further improvement in EASI scores after W8 until W24 [11], and after 1 month until 6 months [12], respectively, our study revealed significant continued improvement in clinical scores from W10 to W16. One possible reason is that our study had higher baseline EASI scores (29.0 ± 16.2) compared to the other two studies (19.6 ± 13.9 and 19.23 ± 3.03), suggesting the necessity of completing the treatment until W16 for pediatric AD patients, at least for those with more severe eczematous lesions.

We detected a significant reduction in eosinophils in the small subset of children with eosinophil level evaluations before and after dupilumab treatment initiation, which is in line with findings in adults and adolescents [13]. Moreover, we found that dupilumab was effective in pediatric AD patients, regardless of the age at onset, sex, atopic comorbidities, and eosinophils, and total IgE levels increase. Furthermore, our regression analysis of EASI improvement showed that the variable of early age at atopic dermatitis onset may negatively correlate with treatment efficacy

Table 2: Real-world effectiveness of dupilumab therapy in pediatric patients.

Scores	Baseline		W4		W10		W16	
	N	Value	*N*	Value	*N*	Value	*N*	Value
EASI, mean ± SD	39	29.0 ± 16.2	36	16.7 ± 9.6****	32	9.0 ± 6.2****	30	5.1 ± 4.7****
EASI 50, *n* (%)		N/A		9 (25.0)		26 (81.3)		27 (90.0)
EASI 75, *n* (%)		N/A		0 (0)		13 (40.6)		22 (73.3)
SCORAD, mean ± SD	39	68.1 ± 18.5	36	44.7 ± 14.1****	32	28.5 ± 13.6****	30	16.7 ± 11.6****
SCORAD 50, *n* (%)		N/A		3 (8.3)		24 (75.0)		29 (96.7)
SCORAD 75, *n* (%)		N/A		0 (0)		6 (18.8)		16 (53.3)
P-NRS, mean ± SD	39	7.9 ± 1.7	36	5.0 ± 1.7****	32	3.0 ± 1.5****	30	1.9 ± 1.4****
CDLQI, mean ± SD	39	14.2 ± 5.8	36	9.1 ± 5.0****	32	5.0 ± 3.8****	30	2.8 ± 3.3****
POEM, mean ± SD	39	19.6 ± 5.6	36	12.5 ± 4.2****	32	7.1 ± 4.2****	30	3.4 ± 2.7****

N, number of children evaluated; W4, week 4; W10, week 10; W16, week16; SD, standard deviation; N/A, not applicable; EASI, Eczema Area and Severity Index; SCORAD, scoring atopic dermatitis; P-NRS, pruritus numerical rating scale; CDLQI, children's dermatology life quality index; POEM, patient-oriented eczema measure. Superscript: **** $P < 0.0001$, in comparison to baseline by paired-samples *T* test. SCORAD 50 and SCORAD 75: reduction of SCORAD compared with baseline of 50% and 75%, respectively; EASI 50 and EASI 75: reduction of EASI compared with baseline of 50% and 75%, respectively.

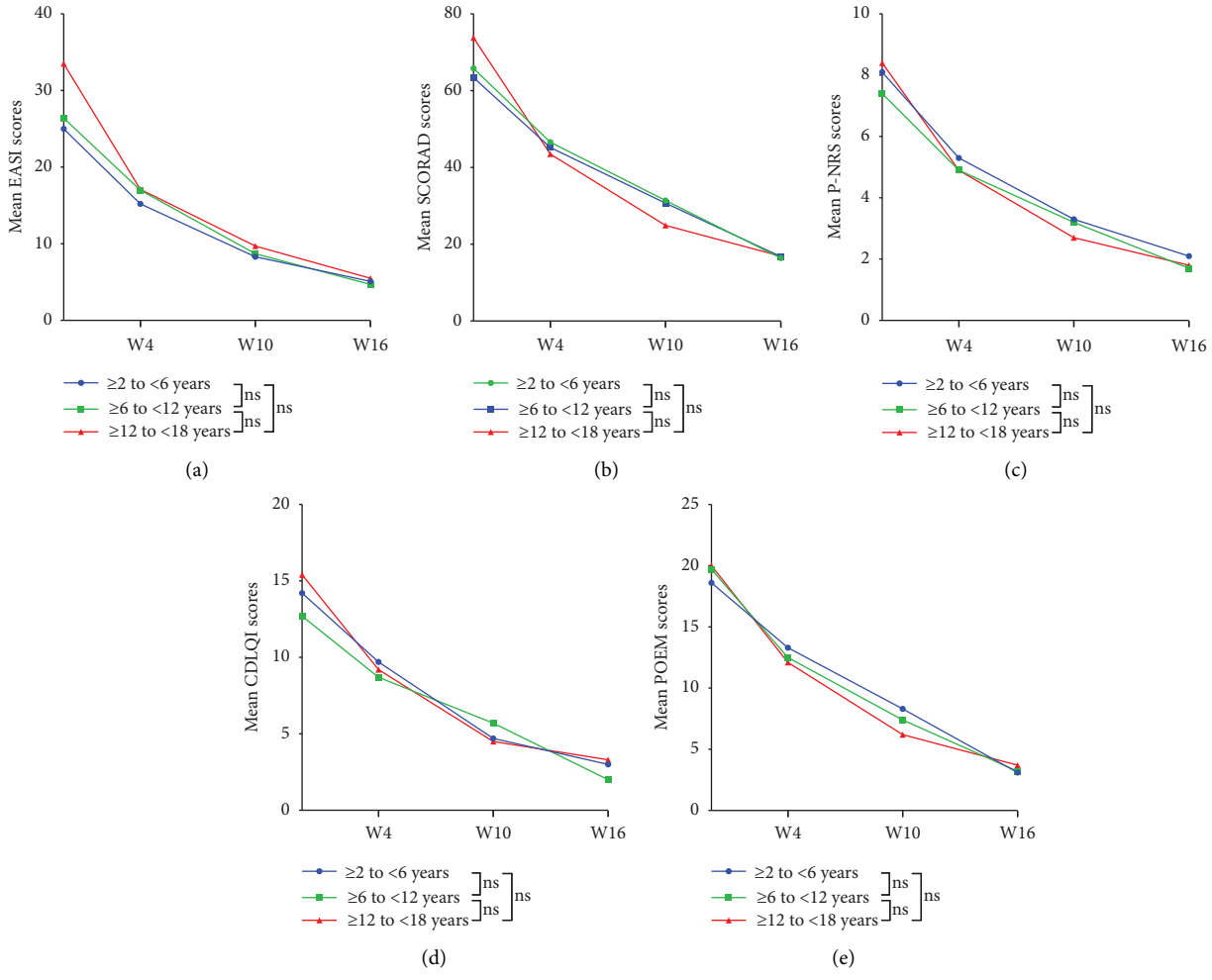

Figure 1: Efficacy outcomes in the three age subgroups (≥2 to <6 years, ≥6 to <12 years, and ≥12 to <18 years): Mean values of the five scales were calculated at baseline and after week 4 (W4), W10 and W16 of dupilumab treatment. The statistical significance was assessed by independent sample t-test, $p < 0.05$; ns, no significance. (a) EASI, eczema area and severity index; (b) SCORAD, scoring atopic dermatitis; (c) P-NRS, pruritus numerical rating scale; (d) CDLQI, children's dermatology life quality index; (e) POEM, patient-oriented eczema measure.

($b = -0.376$, $p = 0.055$), while variables of combined with dupilumab treatment ($b = 0.420$, $p = 0.008$) and early age at dupilumab start ($b = 2.148$, $p = 0.040$) were positively associated with disease improvement. Therefore, these results support early proactive and potent intervention in pediatric AD patients.

Different from previous studies [14–17], we included AD children aged 2 to < 6 years comprising over 20% ratio. In this subgroup analysis, dupilumab showed a comparable therapeutic benefit in all time periods and all clinical AD scores, in comparison with the older age groups (Figure 1). Typically, in the youngest age subgroup receiving dupilumab treatment, the mean percentage and SD changes from baseline in EASI and SCORAD at W16 were 78.5% ± 10.7% and 76.7% ± 10.1%, respectively. The results were superior to those from the LIBERTY AD PRESCHOOL (6 month to < 6 years old) phase 3 clinical trial in dupilumab 300 mg every 4 weeks subgroup, in which the decrease extents were 65.5% ± 5.1% and 51·5% ± 3·5 at W16 [10]. Probably, the lower body weight led to the higher drug exposure in our study that received for better efficacy. The second reason was no-treatment washout before starting dupilumab in contrast to clinical trials.

The overall incidence of treatment-emergent adverse events was 7.7% in our pediatric cohorts during the 16-week dupilumab treatment period (Table 3), which was even lower than previous real-world studies in children aged 6–11 years (12.5%), adolescents (13.5%), and adults (17.5%) [14, 15, 18]. In fact, a larger regimen (Table 3) was partly administrated in our cohorts, which might further prove dupilumab a safe choice in pediatric patients, considering the low occurrence of adverse events. Conjunctivitis was the most commonly reported AE, with incidence rates in real-life studies ranging from 4.95% to 12.15% [12, 19–24], which was observed in 5.1% patients in our study. In the ≥2 to <6 years old group, one child experienced the injection-site reaction after the 2nd injection, which resolved by itself. No systematic infections were observed, similar to previous dupilumab clinical trials in children [9, 10].

This study has some limitations. First, the study was a retrospective observational design, which might have selection bias. Second, a considerable ratio of patients did not receive laboratory examinations alongside the treatment. Finally, due to the small sample size and single-center setting, further multicenter studies with larger sample sizes are warranted to confirm these results in the pediatric population.

5. Conclusion

In summary, our real-world data showed that dupilumab in treating pediatric AD patients, including the 2 to <6 years old subgroup, exhibited a good efficacy showing by the reduction of clinical scores in aspects of disease's severity, symptoms, and quality of life, while possessing a well-tolerated safety profile. Future studies are warranted that will use larger patient populations to collect long-term evidence for using dupilumab to treat the very young, even infants.

Table 3: Treatment-emergent adverse events (TEAEs).

TEAEs	Patients, *n* (%)
Conjunctivitis	2 (5.1)
Reaction injection site	1 (2.6)
Serious adverse events	0 (0)
AE leading to discontinuation of dupilumab	0 (0)

AE, adverse event.

Data Availability

The data supporting the current study are available from the corresponding author upon reasonable request.

Ethical Approval

The manuscript has been read and approved by all the authors. The requirements for authorship as stated earlier in this document have been met. All the authors believe that the manuscript represents honest. UHCT22785.

Conflicts of Interest

The authors declare that they have no conflicts of interest.

Authors' Contributions

Yifei Wang, Chen Shen, Danping Liu, Liu Yang, Changzheng Huang, and Juan Tao contributed conceptualization. Yifei Wang, Chen Shen, Danping Liu, Liu Yang, Changzheng Huang, and Juan Tao provided methodology. Yifei Wang, Chen Shen, Danping Liu, Liu Yang, Changzheng Huang, and Juan Tao did formal analysis and investigation. Yifei Wang, Chen Shen, Changzheng Huang, and Juan Tao wrote and prepared the original draft. Yifei Wang, Chen Shen, Changzheng Huang, and Juan Tao wrote the article and reviewed and edited the article. Yifei Wang, Chen Shen, Liu Yang, Changzheng Huang, and Juan Tao provided funding acquisition. All authors read and approved the final version of the manuscript. Yifei Wang and Chen Shen contributed equally to this work.

Acknowledgments

The authors thank Professor Adam J Adler for critically reading the manuscript. This work was supported by the National Natural Science Foundation of China, Grant/Award Numbers: 81902795 and 82130089.

Supplementary Materials

Supplementary table 1. Dupilumab therapy. Supplementary table 2. Characteristics of children aged 6 months to <6 years. Supplementary table 3. The results of the multivariate regression model. Supplementary table 4. Real-world effectiveness of dupilumab therapy in the three age subgroups. Supplementary figure 1. Changes of biomarkers after treatment with dupilumab. (*Supplementary Materials*)

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