

The changes of eosinophil counts in patients after treatment of Dupilumab: A systematic review and meta-analysis

To the Editor,

The type 2 immune response is mediated by Th2 and ILC2s cells, through the production of type 2 cytokines such as IL-4, IL-13, and IL-5. Multiple cells, including eosinophils, are active by these cytokines. In healthy individuals, eosinophils account for 1%–5% of peripheral blood leukocytes. The type 2 inflammatory diseases include a series of allergic, immune diseases, such as atopic dermatitis, asthma, allergic rhinitis and eosinophilic esophagitis.^{1,2} Dupilumab is a fully human monoclonal antibody, which blocks IL-4/13. Clinical studies have shown optimistic efficacy of Dupilumab, while some studies found that Dupilumab could induce an increase in blood eosinophils.³ Clinicians may be concerned about whether changes in eosinophils may limit the continued use of Dupilumab.⁴ In this study, we evaluated the changes in eosinophil counts after Dupilumab treatment through meta-analysis. Data from different studies were merged, and at different weeks, comprehensive results were obtained.

We searched five databases up to December 31, 2021, to select eligible publications. For included studies, quality was assessed. For randomized studies, the risk of bias tool was applied. For observational studies, Newcastle-Ottawa Scale was applied. The standardized mean difference (SMD) was used to evaluate the change. According to the between-study heterogeneity, fixed or random effect model was selected. The detail of selection and study quality were in Figure S1.

Ten studies were included. Three diseases were included and analyzed through meta-analysis. The detail was in Table 1. At weeks 8, 16, 48, 100, and 148, eosinophil counts showed significant decrease ($P < .05$), which were $SMD = -0.18$ (95%CI: $-0.31, -0.05$); -0.17 (95%CI: $-0.30, -0.04$); -0.37 (95%CI: $-0.43, -0.31$); -0.52 (95%CI: $-0.60, -0.45$); -0.66 (95%CI: $-0.77, -0.54$). At weeks 12 and 24, eosinophil counts showed significant increase ($P < .05$), which were $SMD = 0.20$ (95% CI: $0.07, 0.34$); 0.13 (95% CI: $0.01, 0.26$). At weeks

2, 4, 6, 10, 14, and 52, no significant changes were shown (Figure 1). At weeks 4, 8, 12, and 16, more than five studies were included. The funnel plots all demonstrated asymmetry, indicating the publication bias (Figure S2). From sensitivity analysis, the results were not robust at weeks 8, 16, and 24, because when a certain study was ignored, the significance changed (Figure S3). We further performed subgroup analysis (Figures S4–S6).

The eosinophil counts did not change significantly in the initial weeks. Then, from weeks 8 to 24, the counts decreased and increased alternately. There were some reasons for this phenomenon. In terms of methodology, still not enough studies were included in some comparisons, and the characteristics were different among the studies. At the cellular level, IL-5 mediates the functions of eosinophils mainly,⁵ while Dupilumab targets IL-4 and IL-13. The type 2 response involved multitudinous cells and cytokines, and these factors interact with each other.⁶ When IL-4 and IL-13 were inhibited, the functions of IL-5 may also be affected, and different cytokines may have opposite impact on IL-5. As a result, the eosinophil counts showed the fluctuating tendency. In conclusion, eosinophil counts in patients with type 2 inflammatory disease showed significant change after Dupilumab treatment, and with the treatment prolonged, the counts can be decreased. However, at weeks 48, 100, and 148, each comparison only included one study, so it may not be credible like others. Therefore, high-quality evidence of long-term changes in eosinophils is lacking. Further well-designed studies with larger samples, focusing on a long-term treatment are needed.

Clinically, more attention to eosinophil-related conditions should be paid to patients under Dupilumab treatment, especially for patients with high-baseline eosinophil level.² From our results, eosinophils should be monitored for at least 6 months after Dupilumab treatment. It can be conducted every 2 or 4 weeks, however, long-term strategy still needs further validation.

TABLE 1 Basic characteristics of the included studies

Study ID	Disease	Severity	Type	Country	Age	Dose	Other treatment	Unit	Before treatment		After treatment		
									N	Level ^a	week	N	Level ^a
Wenzel 2013	Asthma	Moderate to severe	RCT	United States	37.8 ± 13.2	300mg qw	Fluticasone-Salmeterol	×10 ⁹ /L	52	0.55 ± 0.19	2	52	0.48 ± 0.29
											4	50	0.52 ± 0.50
											6	49	0.52 ± 0.56
											8	52	0.59 ± 0.58
											12	44	0.72 ± 0.60
Bachert 2016	CRSwNP	-	RCT	International	47.4 ± 9.8	300mg qw	MFNS	×10 ⁹ /L	30	0.41 ± 0.24	16	30	0.39 ± 0.34
Castro 2018 (1)	Asthma	Moderate to severe	RCT	International	47.9 ± 15.3	200mg q2w	Other anti-asthma agents ^b	cells/μL	631	351 ± 348	12	631	468 ± 348
											24	631	435 ± 348
											52	631	371 ± 348
Castro 2018 (2)	Asthma	Moderate to severe	RCT	International	47.7 ± 15.6	300mg q2w	Other anti-asthma agents	cells/μL	632	351 ± 370	12	632	437 ± 370
											24	632	405 ± 370
											52	632	344 ± 370
Olesen 2019	AD	Mainly moderate to severe	Observational	Denmark	median 42	300mg q2w	TCS during flares	×10 ⁹ /L	38	0.55 ± 0.37	4	25	0.91 ± 1.3
											12	27	0.59 ± 0.53
Dupin 2020	Asthma	Severe	Observational	France	median 51	300mg q2w	Other anti-asthma agents	cells/mm ³	54	271.83 ± 281.81	52	51	413.18 ± 485.18
Simpson 2020 (1)	AD	Moderate to severe	RCT	United States and Canada	14.5 ± 1.7	200/300mg q2w	-	×10 ⁹ /L	82	0.71 ± 0.56	4	80	0.71 ± 0.56
											8	80	0.65 ± 0.56
											16	77	0.71 ± 0.56
Simpson 2020 (2)	AD	Moderate to severe	RCT	United States and Canada	14.4 ± 1.6	300mg q4w	-	×10 ⁹ /L	84	0.67 ± 0.48	4	74	0.61 ± 0.48
											8	76	0.61 ± 0.48
											16	72	0.62 ± 0.48
Beck 2021	AD	Moderate to severe	Observational	International	39.2 ± 13.4	300mg qw	TCS and TCI were permitted	×10 ⁹ /L	2638	0.44 ± 0.27	4	2378	0.45 ± 0.28
											12	2167	0.46 ± 0.28

TABLE 1 (Continues)

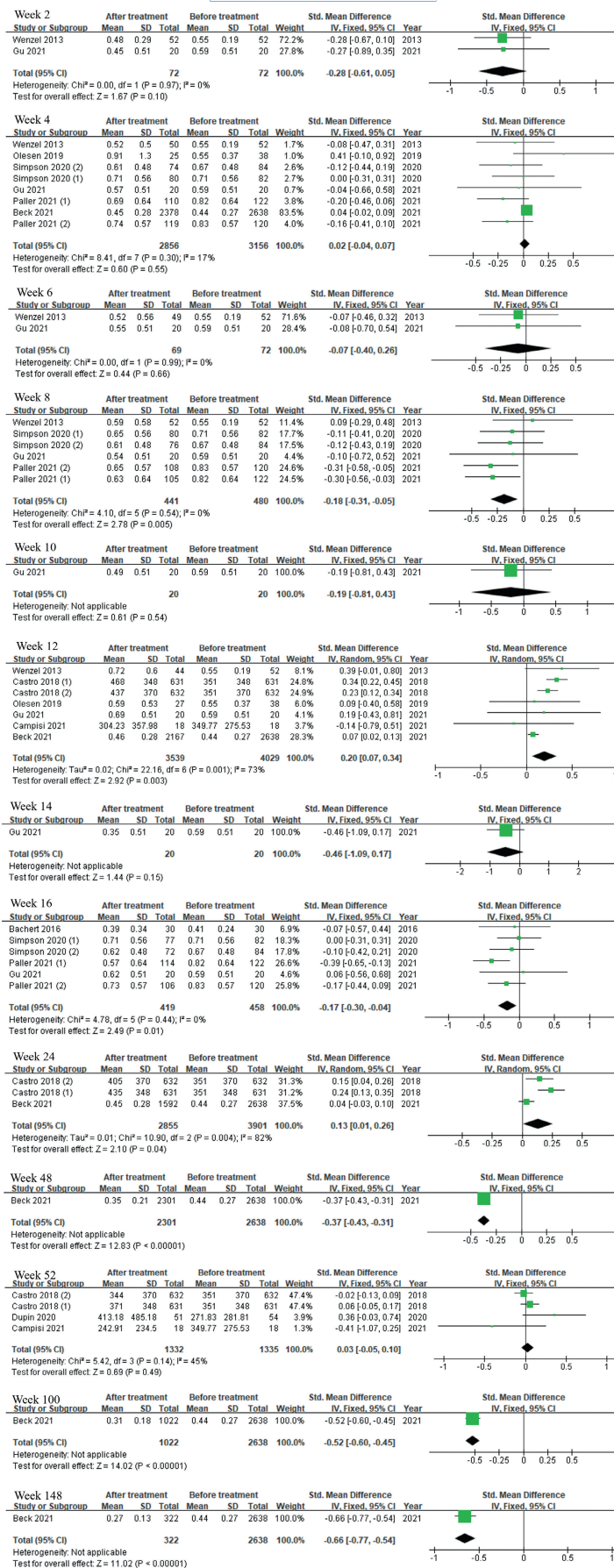
Study ID	Disease	Severity	Type	Country	Age	Dose	Other treatment	Unit	Before treatment		After treatment		
									N	Level ^a	week	N	Level ^a
Campisi 2021	Asthma	Severe	Observational	Italy	53.3±12.4	300mg q2w	Other anti-asthma agents	cells/μL	18	349.77±275.53	24	1592	0.45±0.28
											48	2301	0.35±0.21
											100	1022	0.31±0.18
											148	322	0.27±0.13
									12	18	304.23±357.98		
Gu 2021	AD	Moderate to severe	Observational	China	25.8±12.3	300mg q2w	TCS, TCI and systemic treatments ^b	×10 ⁹ /L	20	0.59±0.51	52	18	242.91±234.50
											2	20	0.45±0.51
											4	20	0.57±0.51
											6	20	0.55±0.51
									8	20	0.54±0.51		
									10	20	0.49±0.51		
									12	20	0.69±0.51		
									14	20	0.35±0.51		
									16	20	0.62±0.51		
Paller 2021 (1)	AD	Severe	RCT	International	8.5±1.7	100/200mg q2w	TCS	×10 ⁹ /L	122	0.82±0.64	4	110	0.69±0.64
Paller 2021 (2)	AD	Severe	RCT	International	8.5±1.7	300mg q4w	TCS	×10 ⁹ /L	120	0.83±0.57	8	105	0.63±0.64
											16	114	0.57±0.64
											4	119	0.74±0.57
									8	108	0.65±0.57		
									16	106	0.73±0.57		

Abbreviations: AD, Atopic dermatitis; CRSwNP, Chronic sinusitis and nasal polypsis; MFNS, Mometasone furoate nasal spray; RCT, Randomized controlled trial; TCS, Topical corticosteroids.

^aIf the original data was not demonstrated in the form of Mean ± SD, transformations were conducted based on the methods from <https://www.math.hkbu.edu.hk/~tongt/papers/median2mean.html> and Handbook for systematic reviews from Cochrane. If the original data was only shown in the figures, the software GetData Graph Digitizer was used to capture the numerical value.

^bOther anti-asthma medications usually included inhaled corticosteroids (ICS), long-acting β₂-adrenergic agonists (LABA), short-acting β₂-adrenergic agonists (SABA), long-acting muscarinic antagonist (LAMA), anti-leukotriene agents.

FIGURE 1 Forest plot of eosinophil counts changes after Dupilumab treatment.



ACKNOWLEDGMENTS

None.

CONFLICT OF INTEREST

None of the authors have a conflict of interest to disclose.

Boyang Zhou 

Surong Liang

Shuai Shang

Lujing Xiang

Linfeng Li 

Department of Dermatology, Beijing Friendship Hospital, Capital
Medical University, Beijing, China

Correspondence

Linfeng Li, Department of Dermatology, Beijing Friendship
Hospital, Capital Medical University, No. 95 Yong'an Road,
Xicheng District, Beijing, 100050, China.

Email: zoonli@sina.com

ORCID

Boyang Zhou  <https://orcid.org/0000-0002-7962-3897>

Linfeng Li  <https://orcid.org/0000-0002-8736-6464>

REFERENCES

1. Hammad H, Debeuf N, Aegerter H, Brown AS, Lambrecht BN. Emerging paradigms in Type 2 immunity. *Annu Rev Immunol*. 2022;40:443-467.
2. Wechsler ME, Klion AD, Paggiaro P, et al. Effect of dupilumab on blood eosinophil counts in patients with asthma, chronic rhinosinusitis with nasal polyps, atopic dermatitis, or eosinophilic esophagitis. *J Allergy Clin Immunol Pract*. 2022. doi:<https://doi.org/10.1016/j.jaip.2022.05.019>. Online ahead of print.
3. Lee DH, Ko HC, Na CH, et al. Real-world experience of long-term dupilumab treatment for atopic dermatitis in Korea. *Ann Dermatol*. 2022;34(2):157-160.
4. Ferrucci S, Angileri L, Tavecchio S, et al. Elevation of peripheral blood eosinophils during dupilumab treatment for atopic dermatitis is associated with baseline comorbidities and development of facial redness dermatitis and ocular surface disease. *J Dermatolog Treat*. 2022;33(5):2587-2592.
5. Shen ZJ, Hu J, O'Neal MA, Malter JS. Pin1 regulates IL-5 induced eosinophil polarization and migration. *Cell*. 2021;10(2):211.
6. Bosteels C, Neyt K, Vanheerswynghe M, et al. Inflammatory Type 2 cDCs acquire features of cDC1s and macrophages to orchestrate immunity to respiratory virus infection. *Immunity*. 2020;52(6):1039-1056.

SUPPORTING INFORMATION

Additional supporting information can be found online in the Supporting Information section at the end of this article.