

Journal Pre-proof

Laboratory changes during dupilumab treatment for atopic dermatitis

D. Flor C. Montero-Vilchez T. Montero-Vilchez S. Arias-Santiago M. Gonçalo



PII: S0001-7310(24)01059-7

DOI: <https://doi.org/doi:10.1016/j.ad.2024.10.059>

Reference: AD 4218

To appear in: *Actas dermosifiliograficas*

Received Date: 23 June 2024

Accepted Date: 13 October 2024

Please cite this article as: Flor D, Montero-Vilchez C, Montero-Vilchez T, Arias-Santiago S, Gonçalo M, Laboratory changes during dupilumab treatment for atopic dermatitis, *Actas dermosifiliograficas* (2025), doi: <https://doi.org/10.1016/j.ad.2024.10.059>

This is a PDF file of an article that has undergone enhancements after acceptance, such as the addition of a cover page and metadata, and formatting for readability, but it is not yet the definitive version of record. This version will undergo additional copyediting, typesetting and review before it is published in its final form, but we are providing this version to give early visibility of the article. Please note that, during the production process, errors may be discovered which could affect the content, and all legal disclaimers that apply to the journal pertain.

© 2024 Published by Elsevier España, S.L.U. on behalf of AEDV.

Sección: Originales**Laboratory changes during dupilumab treatment for atopic dermatitis****Alteraciones analíticas durante el tratamiento con dupilumab para la dermatitis atópica**

Authors: D. Flor^{1*}, C. Montero-Vilchez^{2*}, T. Montero-Vilchez^{3,4,5}, S. Arias-Santiago^{3,4,5}, and M. Gonçalo^{1,6}.

1. Dermatology, University Hospital, Coimbra Local Health Unit, Coimbra, Portugal;
2. Pharmacy Department, Hospital Universitario Virgen de las Nieves, 18012 Granada, Spain
3. Dermatology Department, Hospital Universitario Virgen de las Nieves, 18012 Granada, Spain
4. Instituto de Investigación Biosanitaria ibs.GRANADA, Granada, Spain, 18012
5. Dermatology Area in Medicine Department, Faculty of Medicine, Universidad de Granada, 18012 Granada, España;
6. Faculty of Medicine, University of Coimbra, Coimbra, Portugal

Corresponding author: Trinidad Montero-Vilchez, e-mail address: tmonterov@gmail.com

Abstract

Introduction

Dupilumab is an IL-4 / IL-13 inhibitor monoclonal antibody approved for the treatment of moderate-to-severe atopic dermatitis (AD) with remarkable safety and efficacy profiles. However, former studies have reported an increase in serum eosinophils during treatment, with undetermined clinical significance.

The objective of this study is to evaluate changes in blood eosinophils and other laboratory parameters while on dupilumab.

Methods

We conducted a multicenter, prospective, observational study from 2018 through 2022 with adolescent and adult patients with moderate-to-severe atopic dermatitis treated with dupilumab from *Hospital Universitario Virgen de las Nieves*, Spain, and Coimbra University Hospital, Portugal. Clinical scoring of the dermatitis, complete blood count, total serum IgE and LDH levels were collected at baseline and on weeks 8, 16, 24 and 48.

Results

We included a total of 81 patients (41 women/40 men; mean age of 30.86 ± 12.26 years). Clinical and demographic characteristics were similar across centres. AD severity scales (EASI, SCORAD, ItchVAS and SleepVAS) showed sustained improvement from week 8 of treatment onwards. Eosinophil levels were significantly higher on week 16 ($0.69 \times 10^3/\mu\text{L}$) vs baseline ($0.41 \times 10^3/\mu\text{L}$) ($p = 0.018$) and returned to baseline levels on week 48 ($0.59 \times 10^3/\mu\text{L}$, $p > 0.05$). LDH and IgE levels decreased during the study.

Conclusion

Our study showed a significant clinical improvement of AD but a mild and self-limited increase in eosinophil levels on week 16, not associated with any clinical signs. Therefore, elevated serum eosinophil levels in AD patients on dupilumab does not seem clinically relevant and should not condition treatment withdrawal.

Resumen

Introducción

Dupilumab es un anticuerpo monoclonal inhibidor de la IL-4 / IL-13 aprobado para el tratamiento de la dermatitis atópica (DA) con perfiles de eficacia y seguridad notables. Sin embargo, estudios previos han informado de un aumento de los eosinófilos séricos durante el tratamiento, con un significado clínico indeterminado. El objetivo de este estudio es evaluar los cambios en los eosinófilos en sangre y otros parámetros de laboratorio durante el tratamiento con dupilumab.

Métodos

Se realizó un estudio observacional prospectivo multicéntrico entre 2018 y 2022 con pacientes adolescentes y adultos con DA moderada a grave tratados con dupilumab del Hospital Universitario Virgen de las Nieves, España, y del Hospital Universitario de Coimbra, Portugal. Se recogieron puntuaciones clínicas de la dermatitis, hemograma completo, IgE sérica total y niveles de LDH al inicio y en las semanas 8, 16, 24 y 48 de tratamiento.

Resultados

Se incluyeron 81 pacientes (41 mujeres/40 hombres; edad media de $30,86 \pm 12,26$ años). Las características clínicas y demográficas fueron similares entre centros. Las escalas de gravedad de la DA (EASI, SCORAD, ItchVAS y SleepVAS) mostraron una mejoría sostenida a partir de las 8 semanas de tratamiento. Los niveles de eosinófilos fueron significativamente mayores en la semana 16 ($0,69 \times 10^3/\mu\text{L}$) que al inicio ($0,41 \times 10^3/\mu\text{L}$) ($p=0,018$) y volvieron a los niveles basales en la semana 48 ($0,59 \times 10^3/\mu\text{L}$, $p>0,05$). Los niveles de LDH e IgE disminuyeron durante el estudio.

Conclusión

Nuestro estudio mostró una mejoría clínica significativa de la DA de los pacientes tratados con dupiluman, con un aumento leve y autolimitado de los niveles de eosinófilos en la semana 16, no asociado a ninguna manifestación clínica. Por lo tanto, el aumento de los eosinófilos séricos en pacientes con DA tratados con dupilumab no es clínicamente relevante y no debe condicionar la suspensión del tratamiento.

Keywords

Dupilumab; atopic dermatitis; eosinophils; IgE; LDH.

Palabras clave

Dupilumab; Dermatitis Atopica; Eosinofilos; IgE; LDH.

Introduction

Dupilumab is a human monoclonal antibody that binds to IL-4R- α and IL-13R- α 1 inhibiting IL-4 and IL-13 signalling, which are pivotal for the inflammatory cascade and compromised skin barrier function in atopic dermatitis (AD)¹. Dupilumab acts specifically to downregulate the downstream signalling events that cause the release of pro-inflammatory mediators and the recruitment of immune cells responsible for the clinical signs of AD¹.

Dupilumab became the first biologic agent approved for the treatment of moderate-to-severe AD, with high efficacy and a good safety profile vs former therapeutic options, such as cyclosporine, azathioprine, methotrexate or mycophenolate mofetil^{2,3}. Reported adverse effects include transient local erythema and oedema at the injection site, ocular surface disease, eczematous paradoxical reactions in the head and neck, psoriasis-like eruptions, arthralgia and arthritis and alopecia, with systemic adverse effects being extremely rare².

Elevated blood eosinophil levels while on dupilumab were already noted in clinical trials. However, as there is no formal recommendation to control analytical values while on dupilumab it remains unclear how frequently dupilumab-related eosinophil elevation occurs in real world conditions. In fact, a recent retrospective study reported no significant serum eosinophil elevation, even a normalization of these values while on dupilumab⁴.

The primary endpoint of this study is to evaluate blood eosinophil levels in adolescent and adult AD patients while on dupilumab to define the timing, size, and clinical implications of high eosinophil levels. Secondary endpoints intended to correlate eosinophil levels with other analytical parameters, such as serum IgE and Lactate dehydrogenase.

Methods**Study Design and Participants**

A multicentre ambispective (retrospective and prospective) observational study was conducted from April 2018 through June 2022, in the Department of Dermatology of *Hospital Universitario Virgen de las Nieves*, Granada, Spain and the Department of Dermatology, Coimbra University Hospital, Portugal.

Eligible participants were adolescents (> 12 years old) and adult patients with moderate-to-severe AD scheduled to start treatment with dupilumab for the first time and who signed an informed consent form after being explained the objectives of the study.

Exclusion criteria were cutaneous or systemic infection—namely HIV infection—history of cancer, immunological disease, and use of systemic antibiotics.

In adult patients, dupilumab 300 mg was administered subcutaneously every 2 weeks after a loading dose of 600 mg, whereas adolescents (12-17 years old) received a loading dose of 400mg followed by a 200mg dose every 2 weeks or the adult posology if they weighed > 60kg.

Outcomes and Measures

We collected data on age, sex, age of disease onset, family history of AD, history of asthma, rhinitis, conjunctivitis and food allergies, previous treatments and assessed AD severity at baseline and on weeks 8, 16, 24 and 48 using the EASI (Eczema Area Severity Index), SCORAD (SCORing Atopic Dermatitis), BSA (Body Surface Area), Itch Visual Analogue Scale (VAS) and Sleep VAS scores. At the same time points, fasting venous blood was collected and the following parameters were evaluated: leukocyte count, neutrophils, eosinophils, lymphocytes, monocytes and basophils, total serum IgE and lactate dehydrogenase (LDH).

Statistical Analysis

Descriptive statistics were used to present sample characteristics. Continuous data were expressed as mean (standard deviation) and qualitative data as relative (absolute) frequency. The Shapiro–Wilk test and the Skewness/Kurtosis were used to determine the normality of data distribution and Levene's test was employed to check the homogeneity of variance, Student's t-test for independent samples was used to compare quantitative variables across different populations, and the Student's t-test for paired samples was used to compare differences in parameters across different weeks of treatment. Statistical significance was defined as a two-tailed $p < 0.05$. SPSS version 25.0 (SPSS Inc, Chicago, IL, USA) was used for statistical analyses.

Ethics

This study was approved by *Hospital Universitario Virgen de las Nieves* ethics committee (Analytical biomarkers in patients with atopic dermatitis).

Results

Baseline demographics and clinical characteristics

A total of 81 patients (41 women/40 men); mean age, 30.86 (12.26) years with moderate-to-severe AD; and mean EASI, 28.91 (9.53) were included in the study, 53 (65.4%) from the Spanish hospital and 28 (34.6%) from the Portuguese one, with similar characteristics (Table 1). Disease onset occurred at 6.51 years, approximately 60% had a past medical history of allergic conjunctivitis, asthma, or allergic rhinitis; all patients had been administered previous systemic treatments, most commonly cyclosporin (92.6%), (Table 1).

Clinical changes at the follow-up

All AD severity scales significantly improved after dupilumab (Figure 1). After 8 weeks on dupilumab, a decrease in the EASI (28.91 vs 7.45, $p < 0.001$), SCORAD (61.50 vs 23.87, $p < 0.001$), BSA (29.44 vs 6.62, $p=0.002$), Itch VAS (7.34 vs 3.09, $p < 0.001$), and Sleep VAS (6.57 vs 5.43, $p < 0.001$) scores was observed. This improvement was also significantly on week 48: EASI decreased a mean of 20.05 (9.20) points, $p < 0.001$; SCORAD, 42.13 (36.5), $p = 0.37$; BSA, 24.80 (22.53), $p = 0.043$; and Itch VAS, 4.20 (2.77), $p = 0.028$.

Analytical changes at the follow-up

Changes in blood cell count were reported at the follow-up (Figure 2, Table 2). The levels of eosinophils, which were already high at baseline ($0.53 \times 10^3/\mu\text{L}$; SD, 0.42), did not change significantly within the first 8 weeks on dupilumab. However, a slight increase was reported between baseline and week 16 ($0.53 \times 10^3/\mu\text{L}$ vs $0.69 \times 10^3/\mu\text{L}$, $p = 0.018$). On week 48, serum eosinophils returned to levels that were not significantly different vs baseline ($0.59 \times 10^3/\mu\text{L}$, $p > 0.05$).

LDH and IgE decreased during the studied period (Figure 3). LDH decreased comparing each study period: 234.12 U/L (baseline) vs 192.04 U/L (week 8), $p = 0.003$; vs 195.07 U/L (week 16), $p = 0.005$; vs 181.29 U/L (week 24), $p = 0.043$; vs 191.94 U/L (week 48), $p = 0.003$. IgE decreased mainly from baseline to week 8 of treatment (1274.06 IU/mL vs 647.80 IU/mL; $p = 0.024$). No other analytical changes were found.

Eosinophil levels increased most significantly in 9 patients ($> 1 \times 10^3/\mu\text{L}$), 7 of whom had atopic comorbidities. Two of these patients had asthma and rhinitis and already had high eosinophil counts at baseline (1.27 and $1.09 \times 10^3/\mu\text{L}$), along with a very high total serum Ig E (6193 and 42298 IU/mL). These 2 patients increased eosinophil count on week 8 up to 1.77 and $3.88 \times 10^3/\mu\text{L}$, respectively and the first patient even went up to $4.29 \times 10^3/\mu\text{L}$ on week 16, always parallel to a sharp decrease in IgE down to 1681 and 15803 IU/mL on week 16. Eosinophil values went back to normal after 1 year on therapy in all patients. No clinical signs or progression of atopic comorbidities or eosinophilia-related systemic signs were reported.

In the entire sample there was no statistically significant association between elevated eosinophil levels and IgE levels and any demographic or clinical parameter of these patients.

Discussion

This study evaluated the clinical and analytical impact of dupilumab in a cohort of patients with severe AD and confirmed the expected clinical improvement.

The increase in circulating eosinophils associated with dupilumab therapy have previously been described as transient, mild, and unrelated to therapeutical success. Our results further confirm this trend. Although some patients can grow very high levels of circulating eosinophils, there was no associated progression of atopic or any other systemic signs and no patient had to discontinue therapy. The analysis did not yield any significant clinical impact in patients with dupilumab-induced eosinophil elevation and no correlation was ever found with IgE or LDH levels. Moreover, eosinophil levels went back to baseline values with continuation of therapy.

A similar elevation of blood eosinophils while on dupilumab had been noted in several studies. It has been reported that in AD and chronic rhinosinusitis with nasal polyps, these changes are typically mild (with levels up to 3000 cells/ μL), transient, not associated with clinical symptoms or complications, and unrelated with a reduced efficacy of treatment⁵. Moreover, as in previous research, patients with high levels of eosinophils at baseline are those who experience the greatest increases within the first few weeks on dupilumab. The exception is a case report of eosinophilic pneumonia in a 63-year-old patient with AD⁶. Conversely, a subgroup of patients with severe asthma who started dupilumab developed eosinophilic granulomatosis with polyangiitis⁷.

The mechanism of eosinophil elevation while on dupilumab is still to be elucidated but was attributed to the inhibition of eotaxin-3, VCAM-1, and CCL17/TARC due to IL4/IL-13

blockade, which decreases eosinophil migration without an effect on eosinophilopoiesis⁷. Other authors associated this increase with low number of CD203+ basophils and higher CD23 expression in B cells in a subgroup of AD patients on dupilumab⁸.

Our analysis of results does clarify the pathological mechanism or the risk factors associated with this phenomena, and no statistically significant correlation between eosinophil elevation and demographic, clinical or analytical factors was ever found.

Regarding secondary endpoints, a transient IgE increase while on therapy has been reported in other studies⁴. However, this was not the case in our patients, with IgE steadily decreasing while on dupilumab. Similarly, LDH also decreased progressively, reflecting a decrease in the inflammatory activity associated with clinical improvement as former studies have described⁹.

As far as we know, this multicenter study is the largest study on the impact of dupilumab on eosinophil count in a cohort of patients with severe AD. However, there are some limitations associated with it, namely those inherent to its retrospective and prospective design, such as the heterogeneity of the sample and the limited collection of analytical data.

Conclusions

We conclude that although serum eosinophils do increase in a proportion of AD patients on dupilumab during the early months of therapy, this elevation is self-limited, mild, and not clinically relevant. Therefore, there is no need to discontinue dupilumab. Moreover, despite transient eosinophilia, based on the drug data sheet and the findings of this and other studies, routine laboratory follow-up is deemed unnecessary in patients on dupilumab.

Funding: T.M.V. was supported by a postdoctoral fellowship from Instituto de Salud Carlos III (CM22/00083).

Conflicts of Interest: The authors declare no conflict of interest.

Acknowledgments: This study is a part of Carolina Montero-Vilchez's doctoral thesis at the Clinical Medicine and Public Health program of Universidad de Granada

Ética de la publicación

1. ¿Su trabajo ha comportado experimentación en animales?:

No

2. ¿En su trabajo intervienen pacientes o sujetos humanos?:

No

3. ¿Su trabajo incluye un ensayo clínico?:

No

4. ¿Todos los datos mostrados en las figuras y tablas incluidas en el manuscrito se recogen en el apartado de resultados y las conclusiones?:

Sí

References

1. Harb, H., & Chatila, T. A. (2020). Mechanisms of Dupilumab. *Clin Exp Allergy*, 50(1), 5-14. <https://doi.org/10.1111/cea.13491>.
2. Narla, S., Silverberg, J. I., & Simpson, E. L. (2022, Mar). Management of inadequate response and adverse effects to dupilumab in atopic dermatitis. *J Am Acad Dermatol*, 86(3), 628-636. <https://doi.org/10.1016/j.jaad.2021.06.017>.
3. Seegraber, M., Srour, J., Walter, A., Knop, M., & Wollenberg, A. (2018, May). Dupilumab for treatment of atopic dermatitis. *Expert Rev Clin Pharmacol*, 11(5), 467-474. <https://doi.org/10.1080/17512433.2018.1449642>.
4. Yew YW, Zhao X, Yong AMY. Safety and efficacy of dupilumab in adult atopic dermatitis in Singapore. *Singapore Med J*. 2024 Jan 8. doi: 10.4103/singaporemedj.SMJ-2023-031. Epub ahead of print. PMID: 38189411.
5. Wechsler, M. E., Klion, A. D., Paggiaro, P., Nair, P., Staumont-Salle, D., Radwan, A., Johnson, R. R., Kapoor, U., Khokhar, F. A., Daizadeh, N., Chen, Z., Laws, E.,

- Ortiz, B., Jacob-Nara, J. A., Mannent, L. P., Rowe, P. J., & Deniz, Y. (2022, Oct). 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*, 10(10), 2695-2709. <https://doi.org/10.1016/j.jaip.2022.05.019>
6. Kanata K, Shirai T, Ichijo K, Uehara M. Eosinophilic pneumonia developed after dupilumab administration in a patient with atopic dermatitis. *Respirol Case Rep*. 2023 Jul 18;11(8):e01192. doi: 10.1002/rcr2.1192. PMID: 37469572; PMCID: PMC10352713.
 7. Olaguibel JM, Sastre J, Rodríguez JM, Del Pozo V. Eosinophilia Induced by Blocking the IL-4/IL-13 Pathway: Potential Mechanisms and Clinical Outcomes. *J Investig Allergol Clin Immunol*. 2022 Jun 20;32(3):165-180. doi: 10.18176/jiaci.0823. Epub 2022 May 6. PMID: 35522053.
 8. Čelakovská J, Čermáková E, Boudková P, Andrys C, Krejsek J. The association between eosinophils (CD16+ eosinophils), basophils (CD203+ basophils), and CD23 B lymphocytes in patients with atopic dermatitis on dupilumab therapy: pilot study. *Dermatol Ther (Heidelb)*. 2023 May;13(5):1193-1210. doi: 10.1007/s13555-023-00922-2. Epub 2023 Apr 18. PMID: 37071375; PMCID: PMC10149537.
 9. Zhao, Yan et al; Laboratory Safety of Dupilumab, and Its Effect on Inflammatory Biomarkers, in Chinese Adults With Moderate-to-Severe Atopic Dermatitis: An Analysis of a Randomized, Double-Blind Phase III Study. *International Journal of Dermatology and Venereology* 5(4):p 218-225, December 2022. | DOI: 10.1097/JD9.0000000000000264

Table 1. Sociodemographic and clinical characteristics at baseline

	Total (n = 81)	Granada (n = 53)	Coimbra (n = 28)	P*
Age (years)	30.86 (12.26)	29.74 (12.72)	33.00 (11.25)	0.257
Female, % (n)	50.6% (41)	52.8% (28)	46.4% (13)	0.589
Family history of AD	37.0% (30)	37.7% (20)	35.7% (10)	0.860
Age of disease onset (years)	6.51 (12.47)	7.61 (13.63)	4.28 (9.52)	0.277
Food allergies	12.3% (10)	3.8% (2)	28.6% (8)	0.041
History of asthma	53.1% (43)	32.1% (26)	60.7% (17)	0.036
History of rhinitis	34.6% (28)	28.3% (15)	46.4% (13)	0.690

History of conjunctivitis	19.8% (16)	18.9% (10)	21.4% (6)	0.275
Previous treatment				
- Cyclosporin	92.6% (75)	92.5% (49)	92.9% (26)	0.948
- Methotrexate	43.2% (35)	41.5% (22)	46.4% (13)	0.675
- Azathioprine	27.2% (22)	15.1% (8)	50.0% (14)	0.001
- Mycophenolate mofetil	14.8% (12)	18.9% (10)	7.1% (2)	0.162
- Phototherapy	24.7% (20)	17.0% (9)	39.3% (11)	0.466
- Other biological drugs	1.2% (1)	1.9% (1)	0% (0)	0.471
EASI	28.91 (9.53)	29.71 (9.29)	27.37 (9.97)	0.303
SCORAD	59.84 (12.80)	58.68 (11.87)	63.55 (15.44)	0.275
BSA	40.88 (19.95)	40.71 (20.77)	42.40 (10.71)	0.860
ItchVAS	7.93 (1.98)	8.39 (1.38)	7.60 (2.29)	0.201
SleepVAS	4.68 (3.17)	5.71 (3.31)	3.86 (2.87)	0.073
Leukocytes (x 10³/μL)	8.06 (2.81)	8.06 (2.95)	8.09 (2.39)	0.973
Neutrophils (x 10³/μL)	4.56 (2.18)	4.59 (2.36)	4.48 (1.53)	0.864
Eosinophils (x 10³/μL)	0.53 (0.42)	0.47 (0.36)	0.65 (0.51)	0.081
Lymphocytes (x 10³/μL)	2.34 (0.96)	2.34 (0.96)	2.34 (1.04)	0.978
Monocytes (x 10³/μL)	0.65 (0.63)	0.68 (0.71)	0.57 (0.22)	0.530
Basophils (x 10³/μL)	0.05 (0.03)	0.05 (0.03)	0.06 (0.03)	0.037
Total IgE (IU/mL)	1274.06 (1533.07)	1638.28 (1854.20)	1025.72 (1256.06)	0.238
LDH (U/L)	234.12 (66.93)	223.64 (60.79)	252.37 (74.12)	0.075

Table 2. Eosinophil changes while on dupilumab

	Minimum	Maximum	Mean	Standard deviation
Baseline	0.05	2.23	0.53	0.42
On week 8	0.14	3.88	0.67	0.79
On week 16	0.06	4.29	0.69	0.66
On week 24	0.00	1.70	0.52	0.42
On week 48	0.11	3.91	0.59	0.95

Figure 1. AD scores, from baseline to week 48 showing significant improvement of the EASI (Eczema Area Severity Index), SCORAD (SCORing Atopic Dermatitis), BSA (Body Surface Area) and Itch scores.

Journal Pre-proof

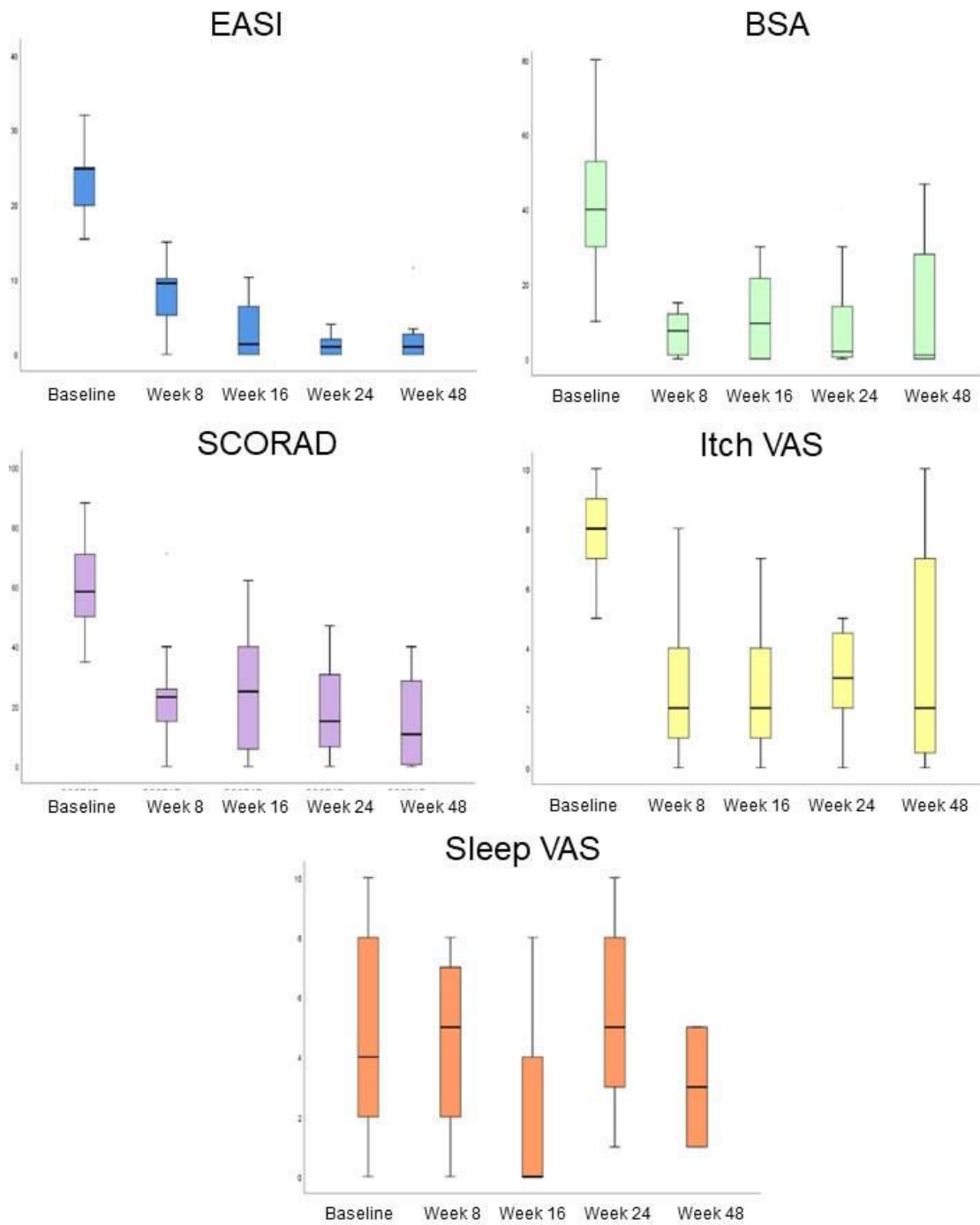


Figure 1

Figure 2. Serum eosinophil values at baseline and on week 48 of treatment.

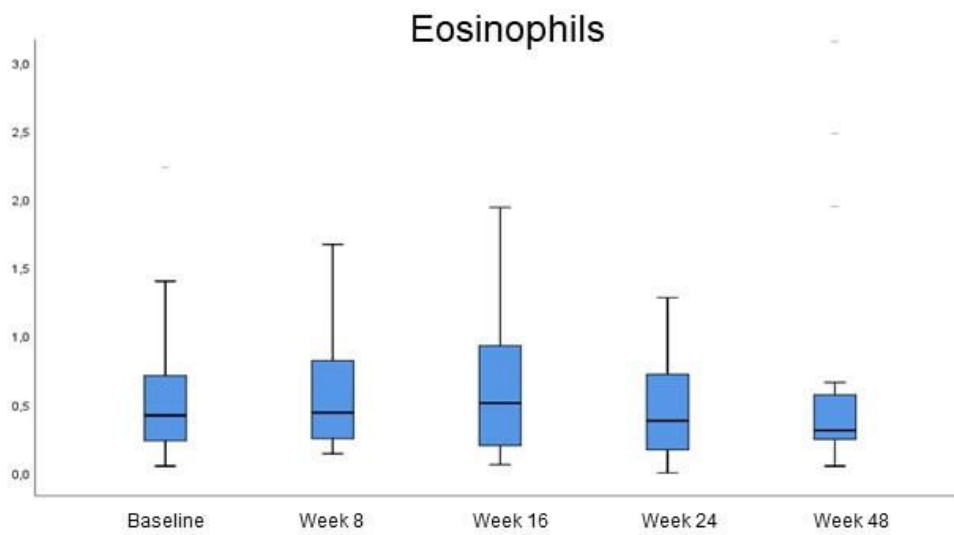


Figure 2

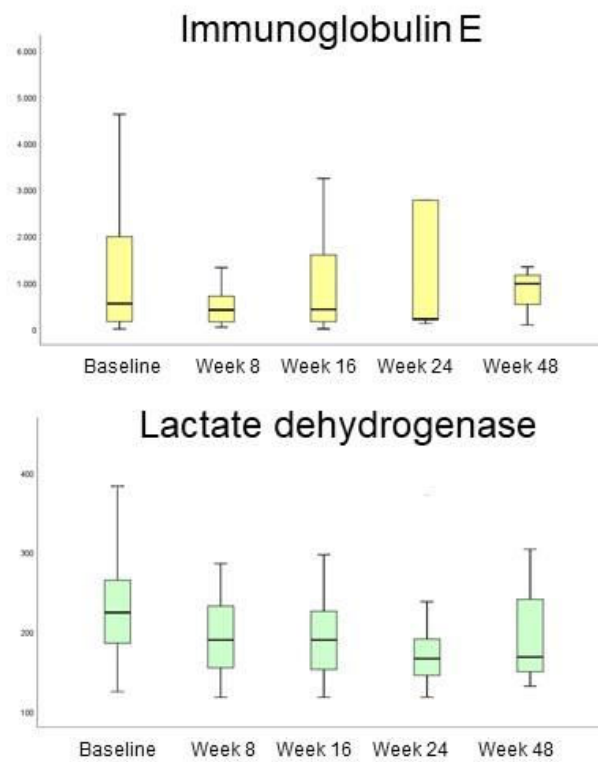
Figure 3. Inflammatory parameters at the follow-up.

Figure 3