SHORT COMMUNICATION

Tralokinumab as an Alternative to Dupilumab in a Patient with Atopic Dermatitis and Asthma who Developed Hypereosinophilia: A Case Report

Ilaria TRAVE[1*], Ilaria SALVI[1], Diego BAGNASCO[2], Aurora PARODI[1] and Emanuele COZZANI[1]
*[1]Section of Dermatology, Department of Health Sciences, University of Genoa, IRCCS – Ospedale Policlinico San Martino, Genoa, and [2]Section of Respiratory Diseases and Allergology, Department of Internal Medicine (DIMI), University of Genoa, IRCCS – Ospedale Policlinico San Martino, Genoa, Italy. *E-mail: ilaria.trave@gmail.com; ilaria.trave@unige.it*
Submitted May 18, 2024; Accepted after revision Sep 9, 2024
Published Sep 19, 2024. DOI: 10.2340/actadv.v104.40800. Acta Derm Venereol 2024; 104: adv40800

Dupilumab and tralokinumab are fully human monoclonal antibodies. The former targets the alpha subunit of the interleukin (IL)-4 receptor, which is shared by the IL-4 and IL-13 receptor complexes, and the latter neutralizes interleukin-13. Dupilumab is currently approved for asthma, moderate-to-severe atopic dermatitis, and chronic rhinosinusitis with nasal polyps (CRSwNP) (1). Tralokinumab was previously studied in trials as a drug for eosinophilic asthma, but with unsatisfactory results, and therefore is not marketed for this disease (2, 3). Both atopic dermatitis and asthma can be associated with increased eosinophil count due to an increase in IL-5 signalling (4).

Moreover, elevation of absolute eosinophil counts (AEC) is one of the most common side effects associated with the treatment with dupilumab and tralokinumab, but there are no studies comparing the frequency of this haematological alteration between the 2 drugs. Hypereosinophilia (HE) is generally referred to as an AE $\geq$1,500/mml on at least 2 different occasions in a 1-month interval (1).

In this paper, we report the case of a patient affected by atopic dermatitis with a hypereosinophilia induced by dupilumab treatment and resolved with a treatment switch to tralokinumab.

CASE REPORT

A 77-year-old woman with a history of hypertension, severe osteoporosis, immune thrombocytopenia, and severe allergic asthma with sudden development of itchy skin lesions presented herself at our clinic. From a month before our observation, her severe eosinophilic asthma was treated with subcutaneous mepolizumab and with a mix of fluticasone and vilanterol inhalation powder, nevertheless with only partial control of the disease.

Clinical examination revealed erythematous, oedematous, and hyperkeratotic skin suggestive of eczema distributed to the upper and lower limbs and the trunk.

Histopathology revealed a spongiotic dermatosis and a psoriasiform pattern with hyperkeratosis, hypergranulosis, and minimal parakeratosis. A perivascular lymphohistiocytic inflammatory infiltrate was present in the superficial dermal layer. Anti-NC16A-BP180, anti-Dsg3, and anti-Dsg1 antibodies in ELISA testing and direct immunofluorescence studies were negative. Patch and prick tests were negative.

Taking into consideration the history of atopy, the clinical presentation of the lesions, the associated symptoms (itch), and the histopathology, a diagnosis of atopic dermatitis was made. The Eczema Area and Severity Index (EASI) score was 24, the pruritus Numerical Rating Scale (pNRS) score was 10, and the Dermatology Life Quality Index (DLQI) score was 25.

Due to the severity of AD, and the simultaneous presence of severe asthma, she was eligible for a switch of treatment, from mepolizumab to dupilumab at standard dosage (an initial dose of 600 mg followed by 300 mg every other week), prescribable for both diseases. In agreement with the pneumologist, a close blood and clinical follow-up was scheduled for eosinophilic asthma, due to the frequent increase of eosinophils in patients treated with dupilumab (4), particularly those switching from anti IL-5 or IL-5r (5). One week after the first injection, she noticed a significant reduction of itching and almost total resolution of eczema (EASI = 10, pNRS = 2, DLQI = 5). The asthma was controlled by the treatment with dupilumab, maintaining ACT levels $\geq$20 and no evidence of exacerbations. After 1 month, complete blood count showed a slight increase of eosinophils ($1.00x10^3$/uL, 10.50%) which became moderate after 4 ($1.50x10^3$/uL, 18.2%) and 6 months of treatment ($2.20x10^3$/uL, 29.9%). After consultation with the pneumologist who was sharing the case with us for the respiratory disease, we stopped administering dupilumab and within 1 month after interruption of the drug, the AEC decreased ($1.30x10^3$/uL, 20.6%).

In December 2024, the patient presented a new severe flare of atopic dermatitis (EASI = 24, pNRS = 10, DLQI = 22) widespread at the trunk and upper limbs. Due to the history of osteoporosis and hypertension, we avoided prescribing oral steroids (which had not been prescribed even before starting treatment with dupilumab), but we chose tralokinumab at standard dosage (one initial dose of 600 mg followed by 300 mg every other week). The eosinophil count remained only slightly above normal limits after 1 month (0.70×10^3/uL, 13.4%), 6 months (0.70×10^3/uL, 12.8%) and 9 months (0.80×10^3/uL, 14%) and she reported a significant reduction of pruritus, eczema (EASI = 5, pNRS = 1, DLQI = 3) with good control of asthma, again without report of exacerbations, oral corticosteroids (OCS) use and maintaining Asthma Control Test (ACT) levels $\geq$20.

DISCUSSION

The main adverse event of the administration of dupilumab and tralokinumab in patients with asthma, chronic rhinosinusitis with nasal polyps (CRSwNP), or atopic dermatitis (AD) is an increase in blood eosinophil levels, not followed by a contextual tissue cells infarction, barring rare cases, as per anecdotal findings in the literature. (5)

Interestingly, patients with eosinophil oesophagitis are reported not to show a transient increase in blood eosinophil counts (6). However, it must be noted that patients with Th2 diseases can spontaneously present an increased blood eosinophil count due to an increase in IL-5 signalling (4).

Generally, hypereosinophilia can be classified as mild (500–1,500/mmc), moderate (1,500 to 5,000/mmc), or severe (>5,000/mmc) (7). This alteration in the blood examination has been reported not only in randomized controlled trials but also, more frequently, in real-life studies. However, treatment-related eosinophilia ≥5,000 cells/mmc occurred in <2% of patients, and eosinophilia >3,000/mmc in from 4% to 14% of patients (8), with few cases having clinical signs and symptoms of organ involvement.

In the case of T2 disease, eosinophils induce inflammation and tissue damage, mainly through the induction of thrombosis and fibrosis (9). The organs usually involved in eosinophilic-mediated damage are the lungs, heart, and nervous system (10).

Although some case reports have described organ damage in patients with increased eosinophils, eosinophil-related organ involvement cannot be accurately predicted on the basis of AEC (11, 12).

The onset of symptoms after starting dupilumab varied from 4 days to 5 months, with most cases occurring after more than 1 month (13). Usually, the detection of eosinophilia during follow-up is associated with increased eosinophils at baseline and a story of asthma and allergic rhinitis.

The pathogenesis of dupilumab-induced blood hypereosinophilia is partially unknown. A transient increase in circulating eosinophils could be due to IL-4/IL-13-mediated inhibition of eosinophil migration from blood into tissues. In fact, IL-4 and IL-13 may regulate the expression of vascular cell adhesion molecule 1 (VCAM-1) on endothelial cells, promoting the transmigration of eosinophils into tissues and inducing the production of chemotactic factors such as eotaxin-1, eotaxin-13, and MCP-4 (14). Moreover, IL-5 signalling, which increases the production of eosinophils by the bone marrow, is usually increased in Th2 diseases and is not inhibited by dupilumab (4). In addition, the steroid-sparing effect of dupilumab contributes to eosinophilia during dupilumab therapy due to the interruption of steroid treatment.

The management of severe hypereosinophilia proposed by other studies is to assess the presence of organ damage using lung function tests, chest radiography, and/or computed tomography (CT) of the chest, serum troponin T, and echocardiography. The frequency and duration of monitoring organ damage and blood count during eosinophilia depends on the individual case. It was also proposed to start a brief low-dose course of systemic steroids (prednisone or prednisolone at a dose of 0.5 mg/kg bodyweight) with a duration that varied from 3 to 10 months to manage the transient increase in blood eosinophils associated with dupilumab (13).

In our case, when the patient developed a moderate hypereosinophilia, we preferred to interrupt the treatment with dupilumab due to her high risk of developing organ damage (e.g., cardiovascular high risk). Moreover, systemic steroid therapy was not integrated with dupilumab due to severe osteoporosis, which she developed following steroid therapy for asthma (4).

We then opted to treat the patient with anti-IL-13 therapy, tralokinumab to be precise, which was able to improve pruritus and AD lesions without causing hypereosinophilia in our patient. One explanation could be that tralokinumab inhibits the signalling of IL-13, but it may not interfere with the signalling of IL-4, which is implied more in the management of concentration of eosinophils in blood (14). Although tralokinumab was reported to increase blood eosinophils in the first months of treatment (15), there are currently no studies that compare the frequency of this side effect in patients treated with tralokinumab and dupilumab, nor which have studied the effect of a treatment switch. Regarding asthma symptoms, the respiratory functionality of our patient improved significantly, despite the reported lack of efficacy of tralokinumab in clinical trials on the forced expiratory volume function (FEV1), asthma control questionnaire (ACQ), and asthma quality of life questionnaire (AQLQ) (15).

In conclusion, we propose that tralokinumab could be considered in any case of severe atopic dermatitis in patients with eosinophilic asthma to control the pruritus and eczema with a reduced risk of hypereosinophilia. More studies should be proposed in order to observe the improvement of eosinophilic asthma in these patients.

The authors have no conflicts of interest to declare.

REFERENCES

1. Ferrucci S, Angileri L, Tavecchio S, Fumagalli S, Iurlo A, Cattaneo D, 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: 2587–2592. https://doi.org/10.1080/09546634.2022.2049588
2. Wollenberg A, Blauvelt A, Guttman-Yassky E, Worm M, Lynde C, Lacour JP, et al. Tralokinumab for moderate-to-severe atopic dermatitis: results from two 52-week, randomized, double-blind, multicentre, placebo-controlled phase III trials (ECZTRA 1 and ECZTRA 2). Br J Dermatol 2021; 184: 437–449. https://doi.org/10.1111/bjd.19574
3. Panettieri RA Jr, Sjöbring U, Péterffy A, Wessman P, Bowen K, Piper E, et al. Tralokinumab for severe, uncontrolled asthma (STRATOS 1 and STRATOS 2): two randomised, double-blind, placebo-controlled, phase 3 clinical trials. Lancet Respir Med 2018; 6: 511–525. https://doi.org/10.1016/S2213-2600(18)30184-X
4. Caminati M, Olivieri B, Dama A, Micheletto C, Paggiaro P, Pinter P, et al. Dupilumab-induced hypereosinophilia: review of the literature and algorithm proposal for clinical management. Expert Rev Respir Med 2022; 16: 713–721. https://doi.org/10.1080/17476348.2022.2090342
5. Eger K, Pet L, Weersink EJM, Bel EH. Complications of switching from anti-IL-5 or anti-IL-5R to dupilumab in corticosteroid-dependent severe asthma. J Allergy Clin Immunol Pract 2021; 9: 2913–2915. https://doi.org/10.1016/j.jaip.2021.02.042
6. Wechsler ME, Klion AD, Paggiaro P, Nair P, Staumont-Salle D, Radwan A, 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; 10: 2695–2709. https://doi.org/10.1016/j.jaip.2022.05.019
7. Kuang FL, Khoury P, Weller PF, Wechsler ME, Klion AD. Biologics and hypereosinophilic syndromes: knowledge gaps and controversies. J Allergy Clin Immunol Pract 2023; 11: 2666–2671. https://doi.org/10.1016/j.jaip.2023.07.026
8. Castro M, Corren J, Pavord ID, Maspero J, Wenzel S, Rabe KF, et al. Dupilumab efficacy and safety in moderate-to-severe uncontrolled asthma. N Engl J Med 2018; 378: 2486–2496. https://doi.org/10.1056/NEJMoa1804092
9. Butt NM, Lambert J, Ali S, Beer PA, Cross NC, Duncombe A, et al. Guideline for the investigation and management of eosinophilia. Br J Haematol 2017; 176: 553–572. https://doi.org/10.1111/bjh.14488
10. Leru PM. Eosinophilic disorders: evaluation of current classification and diagnostic criteria, proposal of a practical diagnostic algorithm. Clin Transl Allergy 2019; 9: 36. https://doi.org/10.1186/s13601-019-0277-4
11. Menzella F, Montanari G, Patricelli G, Cavazza A, Galeone C, Ruggiero P, et al. A case of chronic eosinophilic pneumonia in a patient treated with dupilumab. Ther Clin Risk Manag 2019; 15: 869–875. https://doi.org/10.2147/TCRM.S207402
12. Bjerrum OW, Siersma V, Hasselbalch HC, Lind B, Andersen CL. Association of the blood eosinophil count with end-organ symptoms. Ann Med Surg (Lond) 2019; 45: 11–18. https://doi.org/10.1016/j.amsu.2019.06.015
13. Zhou X, Yang G, Zeng X, Wang L, Xiang J, Zhao J, et al. Dupilumab and the potential risk of eosinophilic pneumonia: case report, literature review, and FAERS database analysis. Front Immunol 2024; 14: 1277734. https://doi.org/10.3389/fimmu.2023.1277734
14. Yamamoto H, Nagata M, Sakamoto Y. CC chemokines and transmigration of eosinophils in the presence of vascular cell adhesion molecule 1. Ann Allergy Asthma Immunol 2005; 94: 292–300. https://doi.org/10.1016/S1081-1206(10)61311-7
15. Iftikhar IH, Schimmel M, Bender W, Swenson C, Amrol D. Comparative efficacy of anti IL-4, IL-5 and IL-13 drugs for treatment of eosinophilic asthma: a network meta-analysis. Lung 2018; 196: 517–530. https://doi.org/10.1007/s00408-018-0151-5