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CASE REPORT

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# Dupilumab after sequential omalizumab and benralizumab failure in T2-high asthma-COPD overlap: A case report

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**Abstract**
Asthma-COPD overlap (ACO) remains therapeutically challenging, and evidence for biologic selection is limited due to the under-representation of overlap phenotypes in trials. We report a T2-high ACO patient who did not benefit from omalizumab or benralizumab but improved with dupilumab. This presents the case of a 67-year-old man with a long-term smoking history, atopy (elevated total IgE with polysensitization), eosinophilia, persistent airflow limitation, and frequent exacerbations despite optimized inhaled triple therapy. Sequential biologics included anti-IgE (omalizumab) and anti-IL-5Rα (benralizumab), with no meaningful reduction in exacerbations or improvement in lung function. After initiating dupilumab at a dose of 300 mg every 2 weeks, the patient reported a rapid improvement in symptoms, with no further exacerbations observed during the follow-up period. Pulmonary function showed a notable increase, with postbronchodilator $FEV_1$ rising from 61 to 72% of the predicted value, and $FEV_1$/FVC ratio improving from 69 to 84.5%. Asthma control scores increased from 12 to 20 by Week 12. Oral corticosteroid therapy was successfully discontinued, and no adverse events requiring discontinuation of dupilumab were recorded. In T2-high ACO unresponsive to anti-IgE and anti-IL-5Rα therapies, IL-4/IL-13 pathway inhibition with dupilumab may deliver a clinically meaningful benefit. Controlled studies are warranted to define its role in overlap phenotypes.


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## Introduction

Asthma–chronic obstructive pulmonary disease overlap (ACO) is characterized by persistent airflow limitation combined with asthmatic and COPD features, typically in smokers with eosinophilic airway inflammation and frequent exacerbations despite optimal inhaled therapy.[1] Because such patients are routinely excluded from randomized trials, evidence-based guidance for ACO remains limited.[2] In type-2-high ACO, biologics directed against IgE (omalizumab) or the interleukin-5 receptor (benralizumab) are extrapolated from severe asthma, yet their benefit rests on small observational cohorts and post-hoc analyses, and real-world data are inconclusive.[3-5] Dupilumab blocks interleukin-4 receptor-α, thereby inhibiting IL-4/IL-13 signaling, and is efficacious in eosinophilic asthma and chronic rhinosinusitis with nasal polyposis.[6] Emerging case reports suggest that it may also improve lung function and symptoms in ACO.[7,8] We describe, to our knowledge, the first ACO patient who failed sequential omalizumab and benralizumab yet achieved sustained clinical and physiological improvement with dupilumab, supporting further exploration of IL-4/IL-13 pathway inhibition in complex, treatment-refractory ACO.

## Case Study

A 67-year-old man had been under regular follow-up at a tertiary respiratory center in western Türkiye for 5 years with a working diagnosis of asthma–chronic obstructive pulmonary disease overlap (ACO). His clinical background included a 60-pack-year smoking history, long-standing allergic asthma, and chronic airflow limitation that remained symptomatic despite guideline-directed inhaled therapy. During the 24 months preceding the current presentation, he required at least two hospital admissions per year for lower-airway exacerbations, each necessitating courses of systemic corticosteroid and antibiotics.

## Phenotypic Profile at Baseline

Laboratory testing revealed blood eosinophil counts that fluctuated between 310 and 370 cells $\mu L^{-1}$ on repeated sampling and a total IgE concentration of 317 IU $mL^{-1}$. Serum allergen-specific IgE assays confirmed polysensitization to *Dermatophagoides farinae*, grass pollens, *Olea europaea*, and Plantago species. These data, together with a postbronchodilator forced expiratory volume in 1 s ($FEV_1$) of 61% predicted and an $FEV_1$/forced vital capacity (FVC) ratio of 69% (persistent airflow limitation), fulfilled current consensus criteria for ACO (Table 1).

## Previous Maintenance Treatment

Before biologic therapy, the patient received a high-dose inhaled corticosteroid with formoterol, ipratropium bromide on a scheduled and rescue basis, and once-daily fixed-dose tablet combining montelukast 10 mg with a second-generation $H_1$-antihistamine. Despite good self-reported adherence, he experienced progressive dyspnea and nocturnal wheeze between exacerbations.

## Therapeutic Course with Sequential Biologics

Omalizumab was initiated in January 2023 at 600 mg subcutaneously every 4 weeks based on his atopic profile. Twelve documented injections were given, some in primary care without concomitant spirometry or biomarker monitoring. No meaningful clinical or functional improvement was observed, and the annual exacerbation rate was unchanged.

Benralizumab (loading 30 mg at 0–4–8 weeks, then every 8 weeks) was started in April 2024 because of persisting type-2 biomarkers and frequent hospitalizations. After six doses, the patient still reported wheezing, dyspnea, and an Asthma Control Test (ACT) score of 12, indicating poor asthma control.

Given the inadequate response to two biologic classes, dupilumab was commenced in March 2025 on the consensus of the Pulmonology and Allergy–Immunology clinics, with an initial 600 mg loading dose followed by 300 mg every 2 weeks. The patient's overall clinical course, biologic treatment periods, and key outcomes are summarized in Figure 1.

## Clinical and Functional Response to Dupilumab

During the first 8 weeks, the patient reported fewer nocturnal symptoms, needed no emergency visits, and markedly reduced his use of systemic corticosteroid. By Week 12, his ACT score had improved from 12 to 20, and no further exacerbations or hospitalizations were documented. Physical

**Table 1** Diagnostic features satisfied in the present case.

| Criterion | Finding in this patient |
|---|---|
| Age ≥ 40 years old | 67 years old |
| ≥ 10 pack-years smoking | 60 pack-years |
| Persistent airflow limitation | Post-BD $FEV_1$ 61% pred; $FEV_1$/FVC 69% |
| Personal history of asthma | Allergic asthma diagnosed > 10 years earlier |
| Atopy/elevated IgE | IgE 317 IU $mL^{-1}$; positive skin-prick test |
| Blood eosinophils > 300 cells $\mu L^{-1}$ | 310–370 cells $\mu L^{-1}$ |
| ≥ 2 exacerbations per year despite therapy | ≥ 2 hospitalizations per year |

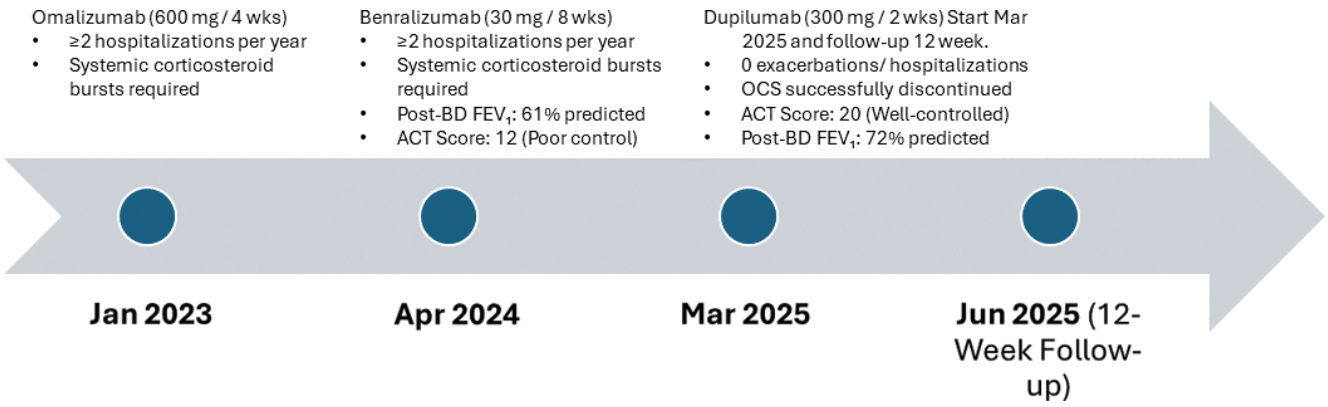
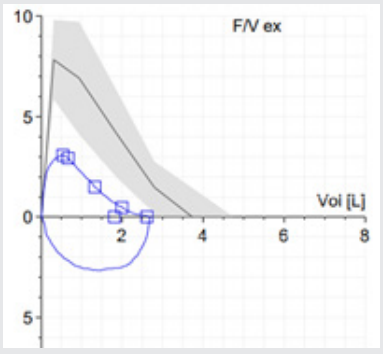
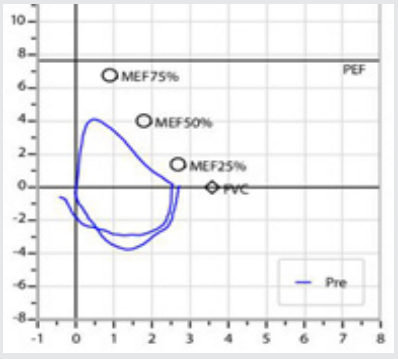



**Figure 1** Timeline of biologic therapy, exacerbation burden, and clinical response.

**Table 2** Comparison of pulmonary function test results at baseline and at 3-month follow-up after dupilumab therapy.




| Parameter PB* | Before dupilumab | | | 3 months after dupilumab therapy | | |
|---|---|---|---|---|---|---|
| | Measured (L) | % Predicted | Z-score | Measured (L) | % Predicted | Z-score |
| FVC (L) | 2.61 | 70 | −1.82 | 2.58 | 67 | −1.63 |
| $FEV_1$ (L) | 1.80 | 61 | −2.25 | 2.18 | 72 | −1.29 |
| $FEV_1$/FVC | 69 | 128 | −1.02 | 84.50 | 103 | 1.15 |
| PEF (L/s) | 3.08 | 39 | −3.92 | 4.10 | 47 | −2.94 |

Values are shown as absolute measurements (L), per cent predicted, and Z-scores based on standard reference equations.
* PB: post-bronchodilator.

examination revealed only faint end-expiratory wheezes, and resting oxygen saturation remained ≥ 95% on room air. C-reactive protein stayed within the reference range, and eosinophil counts normalized. Spirometry indices at baseline and 12 weeks are summarized in Table 2.

In this patient, the diagnosis of ACO was firmly established based on multiple converging clinical and laboratory findings, including advanced age, a significant smoking history, persistent airflow limitation, marked blood eosinophilia, elevated total IgE, and polysensitization to aeroallergens. Taken together, these features provided a robust foundation for the diagnosis and allowed us to approach management with confidence in the underlying classification.

## Discussion

Asthma–chronic obstructive pulmonary disease overlap remains a therapeutic grey zone because virtually all pivotal biologic trials have excluded patients who meet overlap criteria.[1,2] Real-world experience, therefore, guides treatment decisions, particularly for the subset with a type-2-high inflammatory signature. Our patient represents this phenotype, as evidenced by persistent eosinophilia, elevated total IgE and polysensitization.

Omalizumab was chosen first based on atopy. Post-hoc analyses and small observational series suggest that omalizumab can reduce exacerbations in selected ACO cases,[5,9] yet our patient derived no benefit. Benralizumab was tried next to exploit its eosinophil-depleting activity; however, fixed obstruction and overlapping inflammatory mechanisms typical of ACO may blunt its effect.[4,10] These two disappointments underscore the heterogeneity of ACO and the hazard of extrapolating from asthma trials.

Dupilumab antagonizes the shared interleukin-4/interleukin-13 receptor and thus targets a broader segment of the type-2 cascade. Emerging case literature hints at efficacy in ACO settings refractory to narrower biologics.[7,8] Consistent

with those reports, our patient achieved rapid and durable clinical stabilization, accompanied by meaningful gains in $FEV_1$ and FVC and complete cessation of oral steroid bursts. While $FEV_1$ improved significantly, the minor decrease in FVC % predicted (from 70 to 67%) was considered within the range of normal measurement variability and not clinically significant. The chronology—lack of response to two prior biologics followed by stabilization after dupilumab—suggests a drug effect rather than spontaneous remission.

This observation raises two points. First, IL-4/IL-13 blockade may overcome residual type-2 activity that persists despite IgE or IL-5 receptor inhibition. This suggests that in some ACO patients, the IL-4/IL-13 axis may be a dominant driver of persistent inflammation, perhaps via pathways (such as a potential eosinophil rebound after IL-5 pathway blockade or other non-eosinophilic T2 mechanisms) not fully addressed by narrower biologics. Second, biologic sequencing in ACO should be individualized, guided by biomarker evolution and clinical response rather than rigid algorithms.

The report is limited by its single patient data, relatively short follow-up, imperfect adherence documentation during earlier biologic exposure, and the lack of systematic spirometric or biomarker monitoring during the omalizumab therapy, which complicates the interpretation of initial nonresponse. Nonetheless, it widens the anecdotal evidence base for dupilumab in complex overlap disease and may inform future prospective studies.

## Conclusion

In a patient with type-2-high ACO who failed sequential anti-IgE and anti-IL-5R therapy, dupilumab produced rapid and sustained clinical improvement. Although conclusions cannot be generalized from a single case, our findings support further exploration of IL-4/IL-13 pathway inhibition in treatment-refractory ACO.

## Mandatory Disclosure on Use of Artificial Intelligence

The authors declare that AI-assisted tools were used as follows: ChatGPT (OpenAI; model: OpenAI o3), solely for grammar and language editing. All references have been manually verified for accuracy and relevance. All scientific content and factual statements were manually reviewed by the authors.

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## Ethics Statement

Written informed consent was obtained from the patient for publication of his clinical details and imaging.

## Author Contributions

All authors contributed equally to this article.

## Conflicts of Interest

The authors declare no potential conflicts of interest with respect to research, authorship, and/or publication of this article.

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