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ORIGINAL RESEARCH

Dupilumab reduces patient-reported cough and improves quality of life in patients with severe eosinophilic asthma with or without chronic rhinosinusitis with nasal polyps: a real-life prospective study

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Abstract

Background: Cough is a major symptom of asthma and is associated with poor clinical outcomes. However, current guidelines place little emphasis on the crucial relevance of the cough symptom and its treatment. The objective of this study was to assess the impact of dupilumab on chronic cough (CC) in patients with severe eosinophilic asthma (SEA) and chronic rhinosinusitis with nasal polyps (CRSwNP).

Methods: Patients with CC and SEA, CRSwNP, or SEA plus CRSwNP treated with dupilumab were prospectively included. Patients were evaluated before and after 6 months of treatment by collecting Severe Cough Visual Analogue Scale (SC-VAS) scores and the Leicester Cough Questionnaire (LCQ). A total of 67 patients with CC were included.

Results: Both SC-VAS and LCQ significantly improved after 6 months in the whole group (paired *t*-test SC-VAS, mean (SD), from 83.13 (11.54) to 38.21; and LCQ, from 1.98 (0.78) to 4.54 (1.35), both $p<0.001$), and in each disease subset (paired *t*-test, $p<0.001$ in all groups). After treatment, 73% and 82% of patients had a clinically meaningful improvement of SC-VAS and LCQ, respectively.

Conclusion: Dupilumab was found to be associated with significant improvement in CC in 50% (n=10) of patients with SEA, in 73% (n=19) of patients with CRSwNP, and in 62% (n=13) of patients with SEA plus CRSwNP, respectively. In this real-life study, dupilumab significantly reduced CC whilst improving quality of life in patients with SEA with or without CRSwNP. These results support the potential role of dupilumab in the treatment of cough as a treatable trait.

Keywords: chronic cough, chronic rhinosinusitis with nasal polyps, dupilumab and quality of life, severe eosinophilic asthma, unified airway disease.

Citation

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Introduction

Chronic cough (CC), defined as a cough lasting 8 weeks or longer, can have a significant impact on patients' physical, psychological and social well-being.[1] The condition can lead to exhaustion, sleep disturbances and even social isolation. The severity of the impact can vary, with some individuals experiencing more severe complications like rib fractures, urinary incontinence or depression.[1] The frequency, intensity and duration of the cough have been shown to have a significant impact on the patient's overall health-related quality of life (HRQoL).[1] CC can be caused by various factors, including respiratory conditions such as asthma and chronic obstructive pulmonary disease (COPD), allergies and digestive issues. Some of the most common underlying conditions that contribute to this issue include asthma, postnasal

drip, chronic rhinosinusitis (CRS) with or without nasal polyps (CRSwNP/CRSsNP), and gastro-oesophageal reflux disease.[2] Another critical aspect in the management of CC is the frequent poor response to treatment. The management of CC is challenging due to the absence of specific, effective medications approved for treating this condition. Whilst treatments for the underlying causes of CC are often attempted, they may not always be successful and, in some cases, the cause may remain unknown. In relation to the known causes of CC, cough is a major symptom of asthma.[3] It is associated with disease severity, control status, poor clinical outcomes, negative impact on HRQoL, and presence of comorbidities.[3] However, current asthma guidelines place little emphasis on the crucial relevance of the cough symptom and its appropriate treatment.[4,5] Airway mucus hypersecretion is a hallmark of asthma. It has been associated with a greater decline in forced expiratory volume in 1 second (FEV_1), more severe disease, chronic persistent airflow obstruction, and increased exacerbation rates in patients with asthma compared to patients without airway mucus hypersecretion.[6] Furthermore, CC is a common symptom in CRSwNP, and it can be linked to a variety of factors, including asthma.[7]

From an epidemiological perspective, another salient aspect pertains to the coexistence of upper and lower airway involvement in the same patient, a phenomenon referred to as 'unified airway disease' (UAD).[8–10] UAD signifies the concept that upper and lower airway diseases, including allergic rhinitis, CRS and asthma, are interconnected and frequently share a common underlying inflammatory process. This theory posits that, whilst these diseases may manifest in different locations of the respiratory tract, they may ultimately stem from a single pathological cause. Patients with UAD present with a unique set of challenges, attributable to the pronounced severity of the clinical manifestations and the presence of chronic debilitating symptoms, including coughing.

Dupilumab is a monoclonal antibody that functions by targeting and blocking the IL-4 receptor-α (IL-4Rα), thereby impeding the signalling of IL-4 and IL-13.[11] These two cytokines play a pivotal role in the development and progression of various inflammatory conditions. By blocking IL-4 and IL-13 signalling, dupilumab effectively reduces inflammation and related symptoms, as well as improving mucus scores. The potential involvement of IL-13 signalling blockade is becoming increasingly important from a clinical standpoint. IL-13 has been demonstrated to play a pivotal role in mucus hypersecretion by driving goblet cell metaplasia and enhancing the production of mucin 5AC.[12,13] In recent years, the efficacy of dupilumab has been confirmed in a variety of diseases, including severe eosinophilic asthma (SEA), CRSwNP, atopic dermatitis, pruritus nodularis, eosinophilic esophagitis, and COPD.[14] In addition to these well-established therapeutic indications, we would like to highlight the results of our recent work concerning the favourable impact of dupilumab on the 'cough' symptom and related HRQoL aspects.

Methods

This was a multicentre, prospective observational study conducted in four accredited Severe Asthma Clinics in Italy. The study was reviewed and endorsed by the local Institutional Review Board in accordance with the amended Declaration of Helsinki. All patients provided written informed consent for their data to be stored electronically. The study was conducted according to the STROBE guidelines (STrengthening the Reporting of Observational Studies in Epidemiology) for cohort, case–control and cross-sectional studies.

The objective of the present study was to assess the impact of dupilumab on CC symptoms in patients with uncontrolled SEA, CRSwNP or the comorbidity of SEA plus CRSwNP. A total of 67 consecutive outpatients diagnosed with uncontrolled SEA, CRSwNP and SEA plus CRSwNP were prospectively enrolled in the study. These patients were treated with dupilumab at a dosage of 300 mg administered every 2 weeks. The decision to initiate treatment with dupilumab was made subsequent to a multidisciplinary discussion and a meticulous evaluation of patient characteristics, particularly the presence of CC. Subjects with a history of smoking, gastro-oesophageal reflux or arterial hypertension treated with protussive drugs, specifically angiotensin-converting enzyme inhibitors, were excluded from the study. Patients diagnosed with either SEA, CRSwNP or SEA plus CRSwNP who were treated with dupilumab were included in this prospective study from 1 January 2022 to 31 December 2023 (Table 1).

The preliminary patient evaluation was conducted using conventional investigative methods, encompassing an array of procedures such as familial and personal medical histories, pathological medical histories, pulmonary function tests, eosinophil counts, fractional exhaled nitric oxide levels, skin prick tests, serum-specific IgE levels, and high-resolution computed tomography. The Asthma Control Test (ACT) questionnaire was utilized to assess the degree of asthma control. Patients were also assessed for the presence of CRSwNP and/or gastro-oesophageal reflux. In order to overcome the potential confounding effect of tobacco smoke, current smokers were excluded from participation in this study. The diagnosis and severity of asthma were determined in accord-

Table 1. Patient baseline demographic characteristics.

	SEA (*n*=20)	CRSwNP (*n*=26)	SEA plus CRSwNP (*n*=21)
Mean age/age range, years	51.8/35–71	50.2/32–71	53.8/39–72
Men/women	8/12	11/15	10/11
BMI, kg/m^2	23.0 (16.9–32.8)	22.4 (15.2–31.3)	24.1 (18.2–33.5)
Smoking status (never/former)	13/7	14/12	12/9
Atopic status, atopic (%)	8 (40.0%)	8 (30.8%)	9 (42.8%)
Age of asthma onset, years	34 (7–59)	NA	28 (11–56)
Duration of asthma, years	19 (2–54)	NA	17 (12–55)
LABA use	20 (100%)	NA	21 (100%)
ICS use	20 (100%)	NA	21 (100%)
LAMA use	14 (70%)	NA	13 (62%)
LTRA use	8 (40%)	NA	11 (52.4%)
Sustained-release theophylline use	0 (0%)	NA	0 (0%)
OCS use (continuous or intermittent)	16 (80%)	23 (88.4%)	19 (90.4%)
Nasal corticosteroid use	1 (5%)	25(96%)	20 (95%)
Antihistamine use	1 (5%)	0 (0%)	1 (4.7%)
History of other biologicals use, *n* (%)	2 (10%)	0(0%)	0 (0%)
FENO, ppb	38.6 (10–94)	NA	42.3 (18–119)
Pre-bronchodilator FEV_1, % predicted	89 (44–117)	NA	86 (41–128)
BEC, /mL	327 (98–951)	205 (65–663)	358 (121–874)
Serum total IgE, IU/mL	129 (8–1214)	NA	196 (23–1428)
Asthma Control Test	18.67 (4.95)	NA	16.43 (2.86)
Unscheduled physicians' visit in the previous year, times	1.0±3.0	1.0±2.3	2.0±2.6
Hospitalization in the previous year, times	0.4±0.7	0.3±0.9	0.5±0.9

BEC, blood eosinophil count; BMI, body mass index; CRSwNP, chronic rhinosinusitis with nasal polyps; FeNO, fractional exhaled nitric oxide; FEV_1, forced expiratory volume in the first second; ICS, inhaled corticosteroids; IgE, immunoglobulin E; LABA, long-acting beta-agonists; LAMA, long-acting muscarinic receptor antagonists; LTRA, leukotriene receptor antagonists; NA, not applicable; OCS, oral corticosteroids; SEA, severe eosinophilic asthma.

ance with the Global Initiative for Asthma guideline. The diagnosis of CRSwNP and allergic rhinitis was made by otorhinolaryngologists and allergologists with considerable expertise in these fields. The study participants were prescribed baseline asthma-controlling medications and treatments for comorbidities, including CRSwNP and allergic rhinitis, which were continued throughout the study. Patients were evaluated before and after 6 months of dupilumab treatment by collecting Severe Cough Visual Analogue Scale (SC-VAS) scores (reduction of ≥30 mm considered as clinically meaningful, range 0–100 mm) and the Leicester Cough Questionnaire (LCQ) to assess the severity of the cough (≥1.3-point increase considered clinically meaningful, range 19–133).[15,16]

A total of 67 patients with CC were included in the study. The sex distribution amongst the participants was as follows: 43% men and 57% women, with a mean age of 50.5 years (range 32–72 years). A total of 20 patients had SEA, 26 had CRSwNP, and 21 had SEA plus CRSwNP. A meticulous examination revealed no statistically significant disparities in age, sex or atopy amongst the three groups ($p>0.05$).

Statistical analysis

The data are summarized using percentages, means, and standard deviations or medians. The assessment of variations in time of the quantitative characteristics was conducted using a Student's *t*-test or a non-parametric Wilcoxon test for paired data, in accordance with the results of the Shapiro–Wilk test of normality on the

differences. Furthermore, for quantitative characteristics, the 95% confidence intervals for the difference of the means (or of the medians) are reported. McNemar's χ^2 test was employed to assess variations of the dichotomous variables in a two-dimensional contingency table. The statistical significance was set at $p<0.05$. The Wilcoxon signed-rank test was employed to analyse paired data before and after the observation time. Spearman's method was employed to assess the potential correlations between the variables under study. The analysis of the data was conducted using the statistical software R and GraphPad Prism (San Diego, CA, USA).

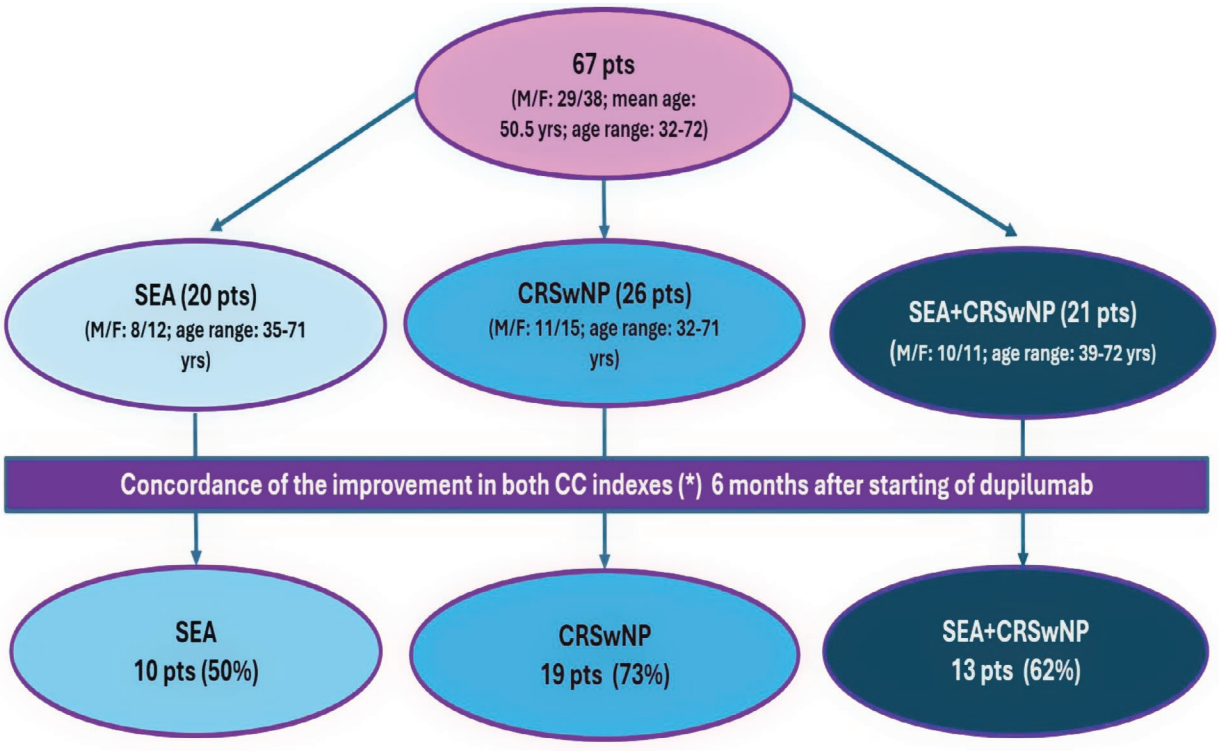
Results

Amongst the 67 patients included in this study, the subgroup of those with SEA plus CRSwNP had the highest mean age (53.8 years), the highest body mass index (24.1), was more frequently atopic (42.8%), took oral corticosteroids more frequently (90.4%), and had higher levels of fractional exhaled nitric oxide, blood eosinophil count, and worse asthma control defined by more frequent exacerbations, hospitalizations, and lower ACT scores (Table 1).

After 6 months of treatment with dupilumab, both the SC-VAS and the LCQ scores demonstrated statistically and clinically significant improvement across the study cohort. Specifically, the mean (SD) SC-VAS score decreased from 83.13 (11.54) at baseline to 38.21 post-treatment, whilst the LCQ score increased from 1.98 (0.78) to 4.54 (1.35), indicating a substantial reduction in cough severity and associated impact on HRQoL (paired *t*-test, $p<0.001$ for both).

These improvements were consistent across all disease sub-groups, including patients with SEA, CRSwNP, and those with SEA plus CRSwNP, with all sub-groups showing statistically significant changes from baseline (paired *t*-test, $p<0.001$ in each group) (Figures 1 and 2).

Figure 1. Dupilumab reduces patient-reported cough and improves quality of life in patients with SEA, CRSwNP and SEA plus CRSwNP comorbidity: concordance of the improvement in both CC indexes (*) 6 months after starting dupilumab treatment.

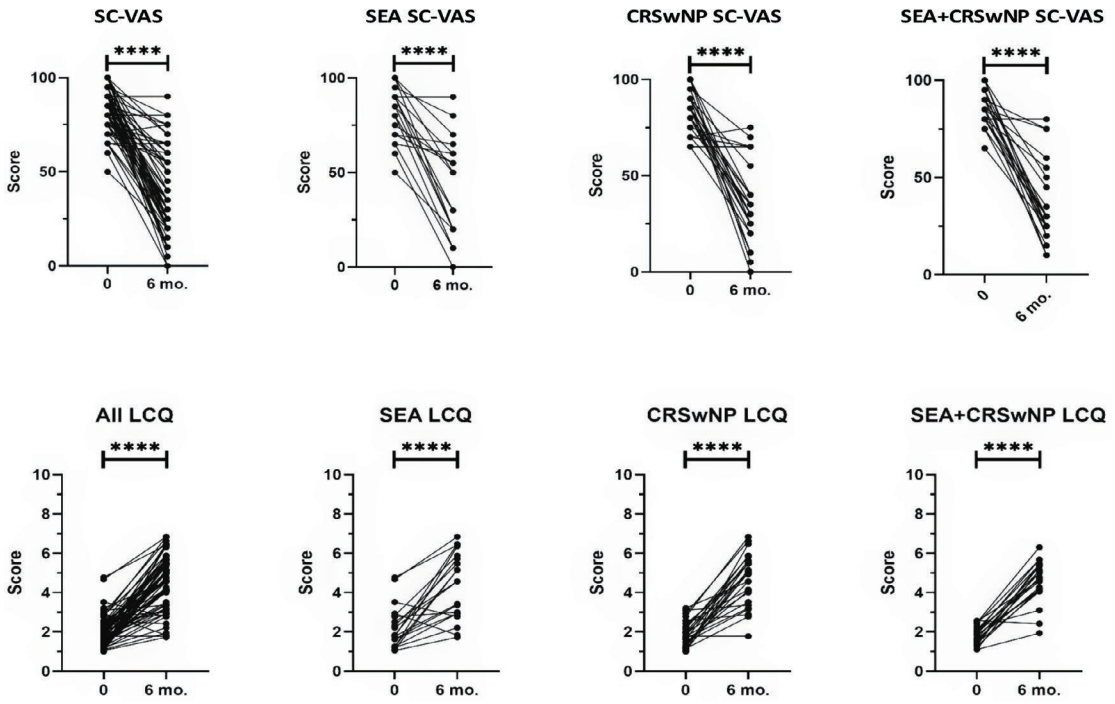


(*) SC-VAS score (0-100 mm): a SC-VAS reduction ≥30 mm was considered as clinically meaningful.

LCQ: clinicians may consider a ≥1.3 point increase in the LCQ total score as clinically meaningful.

CC, chronic cough; CRSwNP, chronic rhinosinusitis with nasal polyps; LCQ, Leicester cough questionnaire; SC-VAS, severe cough visual analogue questionnaire; SEA, severe eosinophilic asthma.

Figure 2. Both SC-VAS and LCQ significantly improved after 6 months of dupilumab in the whole group (paired *t*-test SC-VAS, mean (SD), from 83.13 (11.54) to 38.21; and LCQ, from 1.98 (0.78) to 4.54 (1.35), both $p<0.001$), and in each disease subset (paired *t*-test, $p<0.001$ in all groups).



CRSwNP, chronic rhinosinusitis with nasal polyps; LCQ, Leicester Cough Questionnaire; SC-VAS, Severe Cough Visual Analogue Scale; SEA, severe eosinophilic asthma.

Discussion

In this real-life study, a 6-month course of dupilumab was found to be associated with a significant reduction in CC in patients diagnosed with SEA, CRSwNP, and SEA plus CRSwNP. Additionally, the study indicated an improvement in HRQoL.

Clinically meaningful improvement, defined by established minimal important difference thresholds for SC-VAS and LCQ, was achieved in 73% and 82% of patients, respectively. These thresholds, derived from established benchmarks in cough research, confirm that the majority of patients not only exhibited statistical improvement but also experienced perceptible and meaningful benefits in daily life.[17] These outcomes suggest that dupilumab not only reduces the intensity of CC but also leads to a marked enhancement in HRQoL for the majority of patients. When analysed by disease phenotype, the proportion of patients achieving concordant improvement in both SC-VAS and LCQ scores was 50% (n=10) in the SEA group, 73% (n=19) in the CRSwNP group, and 62% (n=13) in the SEA plus CRSwNP group.

Sub-group analyses then revealed further nuanced differences in response rates. These findings suggest that patients with upper airway involvement, either in isolation or in conjunction with asthma, may demonstrate a heightened response to dupilumab treatment, manifesting as a significant alleviation of CC symptoms. This phenomenon may be attributed to the augmented involvement of type 2 (T2) inflammatory pathways within the upper airway, which are effectively targeted by dupilumab through IL-4 and IL-13 receptor blockade.

The uniformity of these outcomes across the entire study population serves to substantiate the therapeutic efficacy of dupilumab. Of particular significance is the observation that the documented enhancements were not limited to a specific disease phenotype. The results demonstrated statistically significant improvements in both SC-VAS and LCQ scores for all groups compared to the baseline (paired *t*-tests, all $p<0.001$). This finding underscores the broad applicability of dupilumab in managing cough symptoms in patients with diverse manifestations of T2 inflammatory airway disease.

The parallel and concordant improvement across both symptom severity (SC-VAS) and HRQoL (LCQ) serves to strengthen the validity of these results. The robust response rates observed in patients with concomitant upper and lower airway inflammation further substantiate the hypothesis of a UAD model. This model posits

that systemic modulation of T2 inflammation can result in multisystem symptom improvement, including cough, a manifestation that is frequently disregarded in conventional disease assessments.

The findings, when considered collectively, offer substantial evidence supporting the efficacy of dupilumab in markedly reducing the burden of CC in patients diagnosed with T2 inflammatory airway diseases. The consistent improvement across both objective and patient-reported outcomes, the high rates of clinical response, and the efficacy across multiple disease phenotypes support the therapeutic value of dupilumab in this context. This benefit is particularly relevant for patients who suffer from refractory cough despite conventional treatments, positioning dupilumab as a promising and targeted intervention for a symptom that substantially affects HRQoL but is often difficult to treat.

The impact of dupilumab on the cough symptom observed in this study is likely associated with the documented favourable effect of dupilumab in reducing mucus plugs and airway hypersecretion.[12,13] Indeed, dupilumab has been shown to significantly reduce mucus plugging in patients with uncontrolled, moderate-to-severe asthma. A multitude of studies have demonstrated that treatment with dupilumab leads to a reduction in mucus plug scores and improved airway volume and flow and a decrease in airway inflammation, contributing to better asthma control.[18] Dupilumab, by targeting the IL-4 and IL-13 pathways, effectively reduces airway inflammation, a key factor in mucus production and plugging in asthma. The reduction in mucus plugging with dupilumab has been linked to improvements in airway volume and airflow, indicating a positive impact on lung function, as demonstrated in the VESTIGE study.[18] Furthermore, patients with CRSwNP or SEA plus CRSwNP exhibited superior cough symptom control in comparison to patients with SEA. This finding underscores the significance of optimal management of upper airway involvement and the UAD concept.[8–10] Conversely, it is acknowledged that patients undergoing treatment with dupilumab and manifesting both SEA and CRSwNP may exhibit more favourable outcomes compared to those with exclusively SEA.[19–22] The enhanced efficacy observed in patients with comorbid diseases may be attributable to the concomitant regulation of underlying T2 inflammation of CRSwNP and asthma by dupilumab, resulting in simultaneous improvements in both upper and lower airway outcomes[23] Regarding the outcomes of our patients, these links are clearly speculative based on proven and plausible mechanisms of action but are not a direct result of the study.

The present study has some methodological limitations that should be pointed out: the most important one concerns the absence of a control group (as, moreover, is the case in most retrospective real-life studies) treated with a placebo instead of dupilumab. In this regard, we believe that it would have been unethical to exclude patients from dupilumab treatment given the strong and abundant evidence of efficacy. Currently, there are concordant scientific data demonstrating the efficacy of this biologic agent in the treatment of SEA and CRSwNP as well as other T2 conditions. The second limitation is the placebo effect: placebo response in CC studies is notoriously high.[24] The subjective nature of SC-VAS and LCQ makes them particularly susceptible to this effect. However, the presence of the placebo effect is also present in randomized controlled trials (RCTs) and placebo-controlled trials. Another possible limitation is regression to the mean: patients are typically enrolled in these studies when their symptoms are at their peak. A natural improvement (regression to the mean) over a 6-month period cannot be ruled out with certainty. Finally, as in other studies, there are possible confounding cointerventions: baseline medications were continued but patients receiving a new advanced therapy are managed more closely, leading to better adherence to other treatments (e.g. nasal corticosteroids, inhaled corticosteroids), which could independently improve cough. This aspect is also present in most studies and should be interpreted and considered.

The efficacy of dupilumab in asthma and T2 comorbidities is now well established. In this condition, the drug reduces airway inflammation, mucus production and bronchial hyperresponsiveness. These effects lead to a significant reduction in the frequency and severity of cough. RCTs, including the LIBERTY ASTHMA QUEST study, have demonstrated, in addition to the known endpoints for asthma control, an improvement in cough-related QoL in these patients.[25] Additionally, in CRSwNP, a condition often associated with post-nasal drip and upper airway inflammation, dupilumab has been shown (in LIBERTY NP SINUS-24 and NP SINUS-52 RCTs) to reduce polyp size and improve sinus symptoms, thereby alleviating associated cough.[26] Emerging evidence also supports its potential utility in eosinophilic COPD with some case reports and small studies indicating symptomatic improvement.[27] Furthermore, there is growing interest in the off-label use of dupilumab for refractory CC, particularly in individuals with evidence of T2 inflammation, though robust RCT data are still awaited.[28,29]

Some studies have shown significant improvements in cough and sputum production in patients with moderate-to-severe uncontrolled asthma treated with dupilumab. This efficacy is mainly linked to the reduction in hypersecretion and remodelling of airway mucus.[30] Evidence of efficacy on cough and sputum production, as well as overall HRQoL, has also emerged in patients with COPD

and CRSwNP.[31,32] Collectively, these findings suggest that dupilumab may play a valuable role in the management of CC in select patient populations characterized by T2 inflammatory pathways.

It is important to mention the recent approval of the drug gefapixant, a P2X3 receptor antagonist (involved in the cough reflex), which may provide benefit to some patients with chronic refractory or unexplained cough.[33] Its actual efficacy remains to be defined though it seems promising, and there is a risk of adverse events, particularly related to dry mouth and alterations or loss of taste.[34] Furthermore, gefapixant does not act on T2 inflammatory mechanisms as dupilumab does, so it is likely to have only a symptomatic effect.

Conclusion

Dupilumab demonstrated a significant correlation in reducing CC associated with T2 inflammatory diseases, particularly in patients with eosinophilic asthma and CRSwNP. By targeting the IL-4 and IL-13 signalling pathways, dupilumab effectively attenuates airway inflammation and mucus plugging, leading to measurable improvements in cough frequency and severity. This also occurs with the reduction of post-nasal drip and nasal congestion in patients with CRSwNP. These findings underscore the therapeutic potential of dupilumab in managing cough symptoms within the context of T2 immune-mediated conditions. However, its efficacy in CC not driven by T2 inflammation and in coughs of unknown origin remains unproven, and further research is warranted to explore its role in broader aetiologies of CC.

Based on the data from our study, we believe that the potential role of dupilumab in the treatment of the treatable 'cough' in patients with CRSwNP, SEA and UAD should also be considered, as it has been minimally studied but is nonetheless important.

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