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ORIGINAL RESEARCH

Real-World Experience of Dupilumab Treatment for Patients with COPD – A Single Center Prospective Study

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Purpose: Dupilumab was recently shown to be effective in patients with chronic obstructive pulmonary disease (COPD) and type 2 inflammation, while real-world data are missing. We aimed to evaluate the experience of COPD patients treated with Dupilumab.

Patients and Methods: Consecutive patients with COPD treated with Dupilumab were approached and completed a structured interview. Before treatment, all patients had blood eosinophil count ≥300 cells/μL and prior-year exacerbations despite triple inhaler therapy.

Results: Twenty-three subjects were included, with median (IQR) treatment of 320 (280–355) days, median age of 75 years, and 52% female. A decrease in mean annualize exacerbation rate was observed from 3.47 at baseline to 1.55 after treatment (55% reduction). Number of severe exacerbations decreased as well (median 1 vs 0 over the same time frame). There was a decrease in the median COPD assessment test scores (median of 18 vs 15), although FEV1 did not change. One patient had skin-related side effect. Sixty-one percent were content with the treatment, and 74% would recommend it to others with COPD. During interview, patients reported on their need and openness to new and safe treatment options. Using the Global Evaluation of Treatment Effectiveness (GETE) tool, 30% reported on marked improvements following dupilumab. Treatment limitations were costs (48%) and repeated injections (21%).

Conclusion: In this case-series, dupilumab was shown to be well tolerated and was associated with lower rates of exacerbations and improved symptoms. These outcomes were supported by patient reported outcome measurements.

Keywords: chronic obstructive pulmonary disease, biologic therapy, exacerbations, immunologic treatment, eosinophils

Introduction

Dupilumab is a monoclonal antibody that targets the signaling of interleukin (IL) 4 and IL-13 through binding of IL-4 alpha receptor.[1] It is known to be effective for diseases with eosinophilic-predominant inflammation, such as atopic dermatitis and asthma.[2,3] In asthma eosinophilic patients, it was shown to reduce exacerbations by 66%, highlighting its potential for other respiratory diseases with type 2 inflammation. Chronic obstructive pulmonary disease (COPD) is a major cause of morbidity and mortality, yet, new effective treatments are lacking.[4] About 20–40% of patients with COPD have high eosinophil counts,[5,6] making dupilumab a potential therapy.

The BOREAS study was a Phase 3 trial that assessed dupilumab for COPD.[7] It included 939 subjects and found dupilumab to reduce exacerbations, symptoms, and improve quality-of-life. These results were recently validated by the second phase 3 trial – the NOTUS trial.[8] Following the publication of the NOTUS results, dupilumab was approved for uncontrolled COPD by both the European Medicines Agency and the US Food and Drug Administration.

Real-world evidence on dupilumab for COPD is missing and could provide different insights than those from a controlled trial setting.[9] Such evidence was previously published for other biological drugs in patients with COPD and provided important insights on patient characteristics and care.[10,11] Additional evidence exists on the effect of

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biologics in patients with asthma and COPD.[12] However, as these treatments had negative results compared to placebo in randomized controlled trials, they are currently not available for this indication.[13] Still, the importance of real-world evidence should not be undermined. Controlled trials are characterized by stringent inclusion criteria and follow-up, which might limit their generalizability. Real-world data, in-which patients have different diseases and baseline characteristics, can be used to assess generalizability and highlight additional aspects of a new treatment.[14]

The issues mentioned above are especially important in the case of dupilumab and COPD, being the only biologic therapy to receive approval for this indication. For this reason, our primary objective was to evaluate the change in COPD-related outcomes, including exacerbations, symptoms, and pulmonary functions, following the initiation of dupilumab in a real-world setting. We also sought to evaluate the safety of dupilumab and patient-reported outcomes regarding this treatment.

Methods

Study Design

This is a prospective cohort study of patients that were treated with dupilumab for COPD at the pulmonology clinic of Tel-Aviv Sourasky Medical Center between July 2023 and February 2025. The center is a tertiary care center, accepting referrals of complex or severe cases. Following the results of the BOREAS trial, published on the 21st of May 2023, patients in our clinic were offered to receive Dupilumab as an off-label therapy. All subjects signed an informed consent prior to treatment initiation to participate in this prospective registry. The study was approved by our institutional review board (TASMC 0380–24-TLV) and adheres to the declaration of Helsinki.

Study Participants

Eligible subjects had a formal diagnosis of COPD based on the GOLD guidelines criteria (based on post-bronchodilator spirometry)[4] and did not have a concurrent diagnosis of asthma (including asthma-COPD overlap), chronic sinusitis with nasal polyps or any other indication for dupilumab. To be eligible for dupilumab, patients complied with the following criteria:[7] 1) blood eosinophil count ≥300 cells/μL, 2) COPD exacerbations in the prior year while on triple inhaler therapy (long-acting muscarinic antagonists, long-acting beta agonists, and inhaled-corticosteroids), and 3) ongoing respiratory symptoms (either cough, sputum, and/or dyspnea). All subjects completed at-least 6 months of follow-up with a relevant visit to be included and be eligible for outcome analyses.

Treatment Protocol, Evaluation, and Outcomes

Dupilumab was given as an off label therapy, hence, not covered by public health insurance. The first dose was of 600 mg (loading dose), followed by 300 mg every two weeks. Patients were free to decide on the placement of treatment after the second dose (hospital, ambulatory clinic, or home). As per our routine, prior to treatment, patients had an assessment of their CAT score and completed spirometry and blood sample for eosinophil count. Other aspects of our standardized care includes vital signs measurement, assessment of inhaler technique, referral for pulmonary rehabilitation and smoking cessation programs, and treatment adjustment. For the purpose of this study and as per our routine protocol, all patients were interviewed at their visit most adjacent to 12 months of treatment and completed the clinical evaluation for a second time.

Clinical variables were assessed at the baseline and 1-year visits. The variables included COPD-related treatments, smoking status, recommended vaccinations (pneumococcal and yearly influenza), and participation in pulmonary rehabilitation. Patients were also asked about any perceived side effects of the treatment and medical records were also screened to fully evaluate this issue.

For this study, we focused on both objective and patient-reported outcomes. Objective outcomes included the change in moderate-severe COPD exacerbations and post-bronchodilator first second of forced expiration (PB-FEV1, in % predicted). Severe exacerbation was defined as leading to hospitalization. Patient reported outcomes included the following: 1) the COPD assessment test (CAT) score, which is a disease-specific questionnaire with the advantage of being more brief than tools such as the St. George's Respiratory Questionnaire (SGRQ) used in other RCTs,[15] 2) the

Modified Medical Research Council (mMRC) Dyspnea Scale, 3) a 5-point Likert scale questions about treatment satisfaction (Supplementary Material 1), and 4) an open question to describe their experience (Supplementary Material 1). In addition, the Global Evaluation of Treatment Effectiveness (GETE) was used to evaluate the patients' perceived effect of Dupilumab. This is a validated tool previously described with other biologic therapies and use the question "How effective has dupilumab been in controlling your COPD?" with 5 answers between "complete control" to "worsening".[16]

Data Collection and Analysis

Continuous variables were presented as median (inter-quartile range [IQR]) considering their non-normal distribution, as evaluated by the Kolmogorov–Smirnov test. Categorical variables are presented as total (percentage). Number of exacerbations during treatment and in the similar time frame prior to treatment was assessed from medical records. The annualized exacerbation rate (AER) was calculated at baseline and for the follow-up period using the formula: (total exacerbations/total duration of follow-up [days]) X 365. CAT scores were assessed prior to treatment and at the interview for the study. Pre-post analyses were performed using related-samples Wilcoxon Signed Rank tests. Categorical variables were compared by Fisher's Exact tests. All analyses were performed using SPSS, version 28.

Results

Twenty-three patients were included, and their characteristics are shown in Table 1. The cohort's median (IQR) age was 75 (69–81), 52% were females, and median (IQR) peripheral eosinophil count was 350 (300–400). The median time from first treatment to interview was 320 (280–355) days. Two patients (9%) had bronchiectasis and two (9%) were current smokers. Dupilumab was administered at clinic (43%) or home (57%), without missed doses. Most patients (78%) were on single-inhaler triple therapy, five received azithromycin and five received maintenance prednisone at doses of 5–10 mg.

Minor side effects included injection site swelling (n=2) and migraines after the first dose (n=1). One patient suffered from a rash on his lower limbs that has led to dupilumab discontinuation after 6 months. No other side effects were reported and no other patients discontinued the drug (Table S1). One patient died during follow-up after a hip fracture and his latest visit (at 10 months) was included for analysis. No additional patients were lost to follow-up.

Table 1 Characteristics of the Study Cohort

Variable	Study Cohort N=23
Age, median (IQR)	75 (69–81)
Female sex, n (%)	12 (52)
Current smokers, n (%)	2 (9)
Blood eosinophils, median (IQR)[a]	350 (300–400)
Triple inhaler treatment	
FF/UMEC/VI, n (%)	9 (39)
BDP/F/GLY, n (%)	3 (13)
BGF, n (%)	6 (26)
Other non-single inhaler	5 (22)
Azithromycin, n (%)	5 (22)
Prednisone, n (%)	5 (22)
Home oxygen, n (%)	13 (56)
1-year pulmonary rehabilitation, n (%)	8 (35)
Recommended vaccinations, n (%)	17 (74)
Dupilumab treatment setting	
Home, n (%)	12 (52)
Clinic, n (%)	11 (48)

Note: [a]Highest measurement in the 6 months before treatment initiation.
Abbreviations: BGF, Budesonide/Glycopyrronium/Formoterol Fumarate; BDP/FF/G, Beclometasone/Formoterol/Glycopyrronium; FF/UMEC/VI, Fluticasone Furoate/Umeclidinium/Vilanterol.

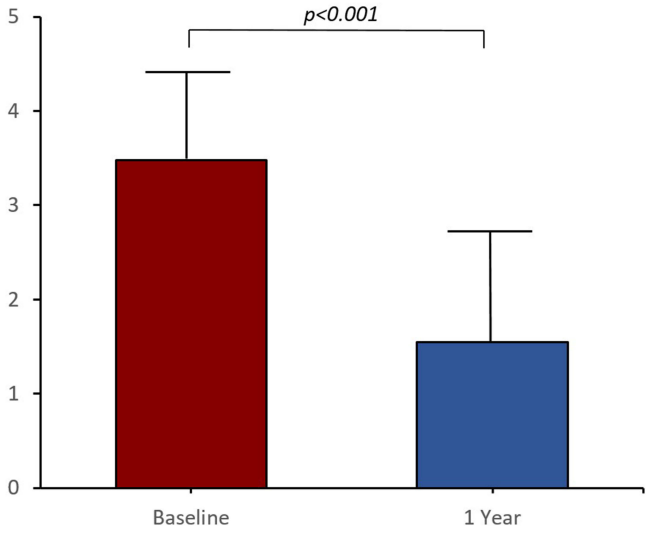

Figure 1 Mean annualized exacerbation rate between baseline (red) and follow-up (blue).

Outcomes are presented in Figure 1 and Table 2. The mean ±SD AER was 3.47 ±0.82 at baseline and 1.55 ±1.29 at follow-up, meaning a 55% reduction in moderate-severe exacerbations. There was also a lower number of severe exacerbations in a similar time frame before and after dupilumab initiation (median [IQR] 1 [0–1] vs 0 [0–1], p=0.040). The CAT score decreased from a median [IQR] of 18 [15–22] before treatment to 15 [12–20] after (p=0.003, Figure 2). The mMRC improved from baseline to follow-up (p=0.005), with 11 patients (48%) having an improvement of at-least 1 point. PB-FEV1 did not change following treatment (48 [37–57] vs 49 [30–60] %predicted, Figure 2). Inhaler treatments also did not change during follow-up. Among the 5 patients on prednisone, two were able to stop treatment and 1 decrease the dose from 10 to 5 mg.

The main structured interview results are shown in Figure 3. Overall, 61% were content with the treatment and 74% would recommend it to others with COPD. Reported treatment-related barriers were costs (48%) and the need for repeated injections

Table 2 Comparison of Outcomes Pre- and Post-Treatment for the Study Cohort (n=23)

Variable	Pre	Post	p
PB-FEV1, %pred.	48 (37–57)	49 (30–60)	0.454
FVC, %pred.	71 (61–77)	72 (63–85)	0.196
mMRC score			
1	2 (9)	6 (26)	0.005
2	8 (35)	10 (44)	
3	9 (39)	5 (22)	
4	4 (17)	2 (9)	
CAT score	18 (15–22)	15 (12–20)	0.003
Phlegm CAT score[a]	3 (3–4)	2 (1–3)	0.011
Exacerbations, amount[b]	3 (2–3)	1 (0–2)	<0.001
Any exacerbation[b]	23 (100%)	17 (74%)	0.022
>1 exacerbation[b]	23 (100%)	10 (44%)	<0.001
Severe exacerbation[c], amount	1 (0–1)	0 (0–1)	0.040
Any severe exacerbation[c]	14 (61%)	7 (30%)	0.075

Notes: [a]Including 15 patients with a high score in the phlegm item of the CAT score (>2). [b]Includes moderate or severe exacerbations. [c]Relates to COPD exacerbations leading to hospitalizations.

Abbreviations: CAT, COPD Assessment Test; PB-FEV1, Post-bronchodilator forced expiratory volume in the first second.

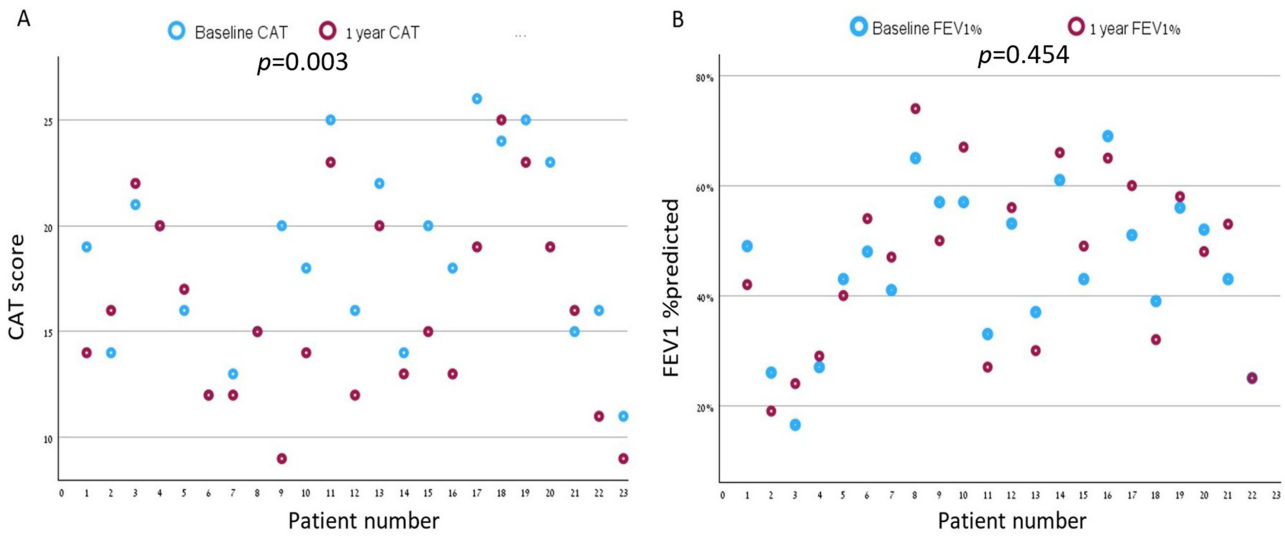

Figure 2 Change in CAT score (panel (**A**) and FEV1 (panel (**B**) from baseline to 1-year per patient.

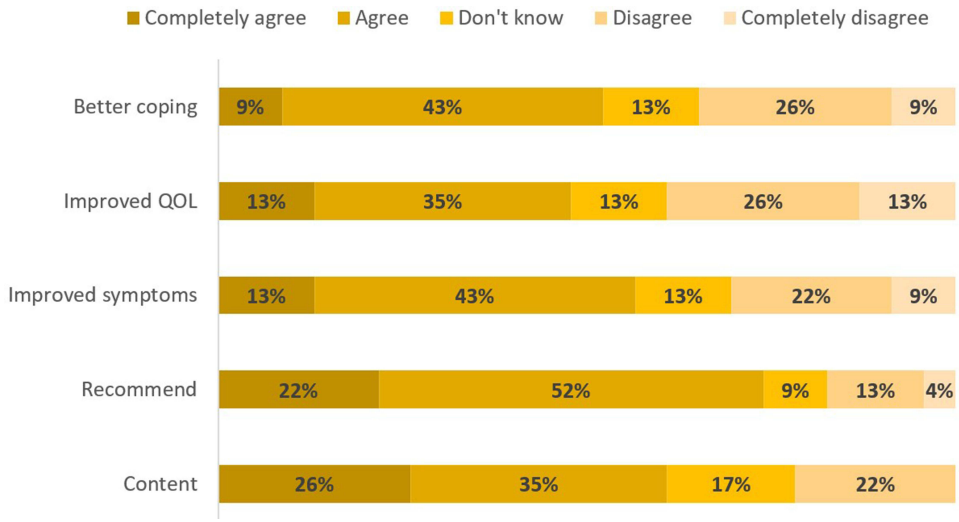

Figure 3 Responses of patients to an open question on their experience with dupilumab, with emphasis on pre-treatment, during treatment, and treatment limitations.

(21%). Using the GETE tool, we found that 30% of subjects rated the treatment effect as complete or marked improvement of COPD, 48% as "Discernible, but limited improvement in COPD", and 22% as "No appreciable change in COPD". Finally, the main theme that was observed in the interview was patients' need of new therapies. Patients highlighted the known safety of dupilumab based on prior knowledge as its main strength and reason they were willing to try it as an off-label therapy (Table 3).

Table 3 Selected Citations on Main Themes From Patient Interviews

Theme	Citation
Pre-treatment	"I was surprised to hear that there is a new treatment for COPD" "I was initially afraid of biologic therapy, thinking it has a lot of side effects" "I just wanted to try something new to improve my symptoms" "I agreed to try the treatment because I knew it was safe"

(*Continued*)

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Table 3 (Continued).

Theme	Citation
Treatment effect	"I stopped expectorate sputum every 5 minutes" "I no longer wake up to expectorate sputum" "I can lift my grandchildren and help my daughter" "The treatment did not change anything, but I still try" "I can walk for longer periods and stopped working only from home"
Limitations	"It is hard to afford the treatment on my own" "I was afraid injecting the drug myself" "I do not want to continue with injections for my entire life"

Another key theme from the interviews was an improvement in sputum production, which was noted by 7 (30%) patients. Using the phlegm item in the CAT score with a cutoff of 3 as a high (worse) score, 15 patients had high phlegm score (overall 21 patients had chronic bronchitis symptoms of any severity). In this subgroup, phlegm scores improved from a median (IQR) of 3 (3–4) to 2 (1–3), p=0.011 (Table 2). In addition, 73% of them were content with dupilumab and had improved symptoms following its initiation.

Discussion

In this case series, we present the novel real-world experience of subjects with COPD treated with dupilumab. Subjects had uncontrolled COPD, defined by exacerbations and symptoms despite triple inhaler therapy, in line with the BOREAS and NOTUS eligibility criteria. Similar to these studies, prescription of dupilumab was associated with a reduction in COPD exacerbations. It was also associated with reductions of CAT score and mMRC, while PB-FEV1 remained unchanged.

The main strength of our study is its real-world design and emphasis on patient-reported outcomes. Real-world evidence has the ability to provide insights into the safety and efficacy of newly approved drugs, especially for patients with characteristics not meeting the criteria for clinical trials.[17] This is highlighted in our study, as many patients from our cohort would not have been included in the phase 3 RCTs of dupilumab. For example, seven patients were over 80 years' old, four had an FEV1 under 30%, seven used home oxygen for more than 12 hours per day, and two patients did not meet the criteria for having chronic bronchitis. Moreover, participating in an RCT often requires filling a daily diary, frequent clinic visits and additional tasks many patients are unwilling to undergo.[18] Considering the above, although an RCT provides the highest level of evidence, its generalizability to real-life may be limited, hence requiring further real-world evidence.

The lack of improvement in PB-FEV1 stands against the outcomes from the BOREAS and NOTUS trials. A possible explanation could be the more severe patient population in our trial with lower baseline FEV1 and the smaller sample size, which was not powered for this evaluation. In addition, we do not believe this should be viewed as a negative outcome. FEV1 decreases over the years, more in patients with COPD, with mean reduction of 21 mL per year according to the ECLIPSE trial.[19] Our cohort naturally included patients with uncontrolled disease that required further treatment; hence, a stability in FEV1 was not expected otherwise and might be counted as a positive outcome, although a matched control group is needed to confirm this hypothesis.

Patient-reported outcomes are inconsistent with regard to biologic therapies for COPD. An improvement in these outcomes was seen in most studies in this field, although it was similar to the improvements in the placebo group.[20,21] This highlights a possible placebo effect that should also be taken into account when evaluating our results.[9] On the other hand, both the BOREAS and the NOTUS trials found improvements in the St. George's Respiratory Questionnaire (SGRQ) scores compared to the control group,[7,8] supporting our results. Setting expectations with patients prior to treatment could be crucial for their satisfaction and self-perceived effect of the drug.[22] A main example from our interviews was of a patient with three exacerbations at baseline who was not satisfied with the treatment even though he had no exacerbations since. Upon further questioning, he noted a lack of improvement in dyspnea, which was the

patient's main treatment goal. In addition, repeated evaluations of patient satisfaction could provide a better reflection compared to a single measurement, which might be adjacent to a respiratory worsening, affecting patients' response.

Reduced sputum was noted by many patients and was the main symptomatic improvement following treatment, as shown with dupilumab in other diseases.[23] A recent RCT by Castro et al among patients with uncontrolled asthma found that dupilumab reduced airway mucus plugging and improved airway volume and flow.[24] Airway mucus plugs have been shown to be associated with increased risk of COPD exacerbations,[25] a possible explanation of dupilumab success. This also supports the results of the BOREAS and NOTUS trials, which included only chronic bronchitis patients. Another key topic raised by participants was the lack of new available treatments. As additional biologic therapies are being studied with promising results, there are still gaps in providing first-line treatments and interventions.[26,27] Smoking cessation and adherence to inhaler therapy with correct inhaler technique are such examples and might be required for eligibility to biologic therapy.

Our study also bears some inherited limitations. First, dupilumab was only offered to patients with uncontrolled disease; hence, a regression towards the mean in this patient population could have led to a decrease in exacerbations, and a randomly selected control group is needed. Second, dupilumab is still not covered for COPD; hence, patients had to pay for the treatment or use a private insurance, leading to a possible selection bias. The tertiary care setting might also confer a similar bias. Finally, the limited follow-up time and small sample size that resulted from the novelty of the treatment could impact our results and not have the statistical power for their assessment.

In conclusion, dupilumab therapy for patients with severe COPD and type 2 inflammation was associated with improved objective and subjective outcomes in a real-world setting. Although a small sample of frequently exacerbating eosinophilic COPD patients, a 55% reduction in annual exacerbations was found. Novel observations, such as the discrepancy between FEV1 results or patient-reported outcomes and prior RCTs and the improvements in sputum, should be the interest of future works. Evidence from larger real-world cohorts and of extended follow-up periods are needed to fully evaluate the effect of dupilumab for COPD.

Data Sharing Statement

The authors confirm that the data supporting the findings of this study are available within the article.

Ethics

All participants signed an informed consent form, including the publication of anonymized responses to the questionnaire and direct quotes. The study was approved by the Tel-Aviv Sourasky Medical Center institutional review board (TASMC 0380-24-TLV).

Author Contributions

All authors made a significant contribution to the work reported, whether that is in the conception, study design, execution, acquisition of data, analysis and interpretation, or in all these areas; took part in drafting, revising or critically reviewing the article; gave final approval of the version to be published; have agreed on the journal to which the article has been submitted; and agree to be accountable for all aspects of the work.

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Disclosure

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