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Dupilumab improves asthma control and lung function in patients with insufficient outcome during previous antibody therapy

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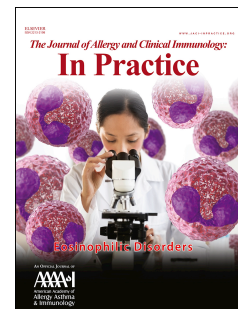
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Highlight Boxes:

What is already known about this topic? Therapy with anti-IL5/IL5R α or anti-IgE antibodies is highly effective in most patients with severe eosinophilic or IgE-dependent asthma. However, in some patients outcome under these therapies is insufficient.

What does this article add to our knowledge? This is the first study assessing the response to the anti-IL4R α antibody dupilumab in patients with insufficient outcome during anti-IL5/IL5R α or anti-IgE therapy.

How does this study impact current management guidelines? Switching to dupilumab appears to be a promising therapeutic option leading to improvement in lung function, asthma control and decrease in OCS use.

Keywords: Severe asthma, dupilumab, type 2 inflammation, IL4, IL5, IL13, IgE

Abbreviations:

IgE Immunoglobulin E

IL Interleukin

ICS inhaled corticosteroid

OCS oral corticosteroid

ACT asthma control test

FeNO fraction of exhaled NO

FEV1 forced expiratory volume in first second

FVC forced vital capacity

MEF25-75% maximum expiratory flow at 25-75% of forced vital capacity

LABA long-acting beta agonist

LAMA long-acting muscarinic antagonist

LTRA leukotriene receptor antagonist

Reff effective airway resistance

Abstract (Word Count: 250)

Background: Biological treatments directed against IgE and IL5 have largely improved outcomes for patients with severe type-2 high asthma. However, a fraction of severe asthmatics shows insufficient treatment outcome under anti-IgE and anti-IL5/anti-IL5 receptor α (anti-IL5R α) antibodies.

Objective: To evaluate whether switching to dupilumab was of benefit in patients with insufficient outcome under previous anti-IgE or anti-IL5/IL5R α therapy.

Methods: We retrospectively analyzed 38 patients that were switched to dupilumab from a previous anti-IgE or anti-IL5/IL5R α medication due to insufficient outcome. We defined response criteria after 3-6 months as an improvement in at least one of the following criteria without deterioration in the other criteria, comparing values under dupilumab to values under previous antibody: 1.increase in asthma control test (ACT) ≥ 3 , 2.reduction in oral corticosteroid (OCS) dose $\geq 50\%$, 3.FEV1 improvement ≥ 150 ml, and classified patients in responders and non-responders.

Results: Switch to dupilumab led to a response in 76% of patients. In the total cohort, ACT score increased by a mean of 2.9 ($p < 0.0001$), while exacerbations decreased significantly ($p < 0.0001$) and number of OCS dependent patients decreased from 15 to 12. Mean FEV1 improved of 305ml ($p < 0.0001$). Median FeNO decreased by -30ppb ($p < 0.0001$), while eosinophil counts increased by 0.17G/l ($p < 0.01$). There were no significant differences in clinical characteristics between responders and non-responders to dupilumab. However, patients with increased FeNO (≥ 25 ppb) during previous antibody were more often responders than patients with low FeNO (< 25 ppb) ($p < 0.05$).

Conclusions: Altogether, we show that a switch to dupilumab in patients with insufficient outcome under previous biological therapy was effective in the majority of patients.

Main Manuscript (wordcount 2907)**Introduction:**

Severe asthma is defined by the ERS/ATS as insufficient asthma control despite high-dose inhaled corticosteroid (ICS) therapy and additional controller medication (long-acting beta agonist (LABA), long-acting muscarinic antagonist (LAMA), leukotriene-receptor antagonist (LTRA) or theophylline) or despite long-term oral corticosteroid (OCS) therapy (2, 3). During the last decades, better knowledge of asthma pathophysiology and the discovery of a type 2 (T2)-signature with soluble mediators like IL5, IL4, IL13 and IgE has led to the development of targeted therapies for severe asthma. Anti-IgE- (omalizumab), anti-IL5- (reslizumab, mepolizumab) and anti-IL5R α -antibodies (benralizumab) have been shown to improve asthma control, reduce asthma exacerbations, reduce oral corticosteroid medication and for anti-IL5/R α -antibodies also to improve lung function (4-9). However, some patients have an insufficient response to anti-IgE or anti-IL5/anti-IL5R α -therapy. In a study performed by Drick et al. 24% of patients treated with mepolizumab were classified as non-responders (10). Further, even if an improvement is observed under a certain antibody, outcome may be judged insufficient in some patients e.g. if oral steroid cannot be tapered off. Recently, dupilumab, a novel antibody blocking the α -subunit of IL4 receptor and thereby inhibiting IL4 and IL13 signaling has been approved for severe asthma as well as for atopic dermatitis and nasal polyps (11-15). Dupilumab reduces asthma exacerbations, improves lung function, reduces type 2 biomarkers, and allows OCS tapering in severe asthmatic patients (11, 12, 16-18). Here, we analyzed the response to dupilumab in patients that previously showed insufficient treatment outcomes under anti-IgE or anti-IL5/anti-IL5R α - therapies.

Methods:*Ethics:*

The study was approved by the local ethics committee (LMU Munich).

Inclusion criteria:

Data was retrospectively collected from the severe asthma outpatient units at the Ludwig-Maximilians-University of Munich and Hanover Medical School. Inclusion criteria were severe asthma as defined by the ERS/ATS consensus statement (2), former anti-IgE or anti-IL5/anti-IL5R α -therapy for a duration of at least three months and a switch to dupilumab in less than six months after discontinuation of anti-IgE-/anti-IL5/anti-IL5R α -therapy. Further, for inclusion asthma control test (ACT) score, steroid dose and lung function follow up data had to be available at 3 to 6 months after initiation of dupilumab.

All patients fulfilled EMA prescription criteria for their previous antibody therapy (anti-IgE or anti-IL5/anti-IL5R α -therapy respectively) as well as criteria for dupilumab. Antibody initiation and switching was performed by the treating physician on an individual basis and solely on clinical grounds. The reasons for switching were recorded. In patients eligible for both anti-IgE and anti-IL5, generally anti-IgE therapy is chosen if clinically allergic triggers are the main driver of disease despite adequate measures of allergen avoidance and anti-IL5/R α is preferentially chosen in patients with late-onset asthma and/or pronounced eosinophilia. However this was a retrospective study and there was no per protocol decision when to start which antibody.

Patient data and treatment:

Patient characteristics, including ACT, asthma exacerbations, pulmonary function tests, IgE values, blood eosinophil levels were collected at baseline (without antibody) and during previous antibody therapy (first antibody). Values with closest proximity, but maximal interval of three months before the timepoint of discontinuation of previous antibody were recorded. Dupilumab therapy was initiated with a loading dose of 600mg subcutaneously and further injections of 300mg every two weeks. Response to dupilumab was reevaluated 3-6 months after initiation of therapy. Again, clinical, laboratory and pulmonary function tests were recorded. Nasal comorbidities (allergic rhinitis, chronic sinusitis, nasal polyps) were recorded as reported by the patient or - if available - as documented in sinus imaging and ENT specialist statement and subjective response during previous therapy and under dupilumab were recorded.

Definition of clinical response to dupilumab:

Patients were classified as responders or non-responders according to changes in ACT, lung function and OCS reduction. Response to dupilumab was defined as at least one positive response criterion without significant deterioration in any other criterion: 1) An increase in FEV1 of at least 150ml. This cutoff was chosen in accordance to the FEV1-changes seen in the phase 3 LIBERTY ASTHMA QUEST trial (17). 2) An increase in ACT of at least 3 points, which was previously suggested as the minimally clinical important difference (19, 20). 3) Reduction of OCS dosage of at least 50% as this was the median reduction observed in steroid reduction trials with dupilumab as well as other biologicals (9, 18, 21). Response of comorbidity was recorded but not defined as response criterion. Significant deterioration was defined as 1) loss in FEV1 of 150ml or more, 2) decrease of ACT of 3 points or more, 3) every increase of OCS dose more than two weeks, 4) increase in exacerbations. Exacerbations were defined as a transient worsening of asthma control, necessitating steroid pulse therapy

for less than two weeks, whereas “increase of OCS dose” was defined as an increase in OCS-dose of more than two weeks. Of note, all criteria were assessed at the same timepoint of reevaluation and patients who needed an increase of OCS dose before the reevaluation timepoint, could have improved ACT score or FEV1 at the reevaluation timepoint due to the increased OCS dose and would still be classified as non-responders.

Statistical Analysis

Data are presented as numbers (n) and percentages. Mean and standard deviation (SD) is shown in case of normal distribution, otherwise median and interquartile range (IQR) is shown. Paired t-test or Wilcoxon signed-rank test were used as appropriate and specified in the according figure legend. P-values < 0.05 were considered statistically significant. Pearson R was used for correlation analysis. Statistical analysis was performed with GraphPad Prism 8 (GraphPad Software, San Diego, CA) and SPSS Statistics 25 (IBM SPSS, Armonk, NY).

Results

In a cohort of 454 severe asthma patients treated with biologics in the participating centers, we identified a total number of 38 patients that were switched from a previous antibody therapy to dupilumab and fulfilled inclusion criteria. 32 patients (84%) were switched to dupilumab from a previous anti-IL5/anti-IL5R α -therapy (mepolizumab (n=11), reslizumab (n=2), benralizumab (n=19)). Six patients were switched to dupilumab from a previous anti-IgE-therapy (omalizumab (n=6)).

The mean age of the cohort was 55 years, 58% were female patients. The median age at asthma diagnosis was 25 years. Sensitization to aeroallergens was found in 76% of patients, and comorbidities were frequent with nasal polyps and allergic rhinitis being most frequent (each 47% of patients) (table 1).

Patients were intensively treated with medium or high-dose ICS/LABA, additional LAMA and/or LTRA at baseline (without antibody), but also during previous antibody therapy with anti-IgE or anti-IL5 (table 2). At baseline 64% of patients were taking prednisone continuously and type-2 biomarkers were increased at median with FeNO of 52ppb, blood eosinophils of 0.41G/l and IgE of 333IU/ml (table 2). Individual patient data shows that 19 out of 38 patients would have been formally eligible for both anti-IgE and anti-IL5 treatment according to EMA prescription criteria and biomarker (table E1).

Compared to baseline without antibody, previous antibody therapy with anti-IgE or anti-IL5/R led to an improvement in several clinical parameters most prominently reduction in the number of patients taking prednisone from 23 to 15 (table 2 and figure 1). Using responder criteria defined above, 42% patients classified as responders to the previous therapy (table

E2). Yet, outcome was judged insufficient and switching to dupilumab was performed due to one or several of the following reasons: insufficient subjective treatment response (n=32, 84%), insufficient improvement in lung function parameters (n=26, 68%), insufficient reduction in asthma exacerbations (n=18, 47%), insufficient response of comorbidities (n=11, 29%), especially no improvement of nasal polyps (n=8, 21%), insufficient reduction in oral corticosteroid dose (n=12, 32%), persistent eosinophilia (n=5, 13%), persistent allergic symptoms (n=2, 5%) and suspected severe side effect of previous antibody (n=1, 3%) (table 3).

Under previous antibody asthma control was poor with a mean ACT score of 14 (SD 5). 21 patients (55%) reported at least one exacerbation during the previous antibody therapy. The calculated annualized number of exacerbations during previous antibody therapy was 0.8 (IQR 0.0-2.4). Lung function was obstructive with FEV1 % predicted of 60% (SD 23), reduced mid-expiratory flow at 25-75% (MEF25-75%) of 32% (SD 21). Residual volume was increased to 144% (SD 34). Under previous antibody therapy markers of T2 high inflammation were partly present with a median FeNO of 55 ppb (IQR 27-102), blood eosinophils of 0.20 G/l (IQR 0.16-0.42) in patients on anti-IgE-therapy and an elevated total IgE of 186 IU/ml (IQR 49-365) in patients on anti-IL5/R α - therapies (table 2).

Response to dupilumab was evaluated 3-6 months after treatment initiation by comparing to the values during the previous antibody therapy. The mean data of the total cohort are presented in figure 1, showing significant improvement of lung function with increase of FEV1 of 305ml (SD 426ml, $p<0.0001$), FVC of 214ml (SD 513, $p<0.05$) and MEF25-75 of 0.384 l/s (SD 0.652). ACT score increased by 2.9 (SD 4.6, $p<0.001$), annualized exacerbations decreased by a median of 0.81/year ($p=0.001$) and the number of patients on prednisone was reduced from 15 to 12 (figure 1A+B). Separate analysis of patients with previous anti-IL5/R α and anti-IgE therapy respectively, showed similar results as the total cohort (figure E1 and figure E2).

Eosinophils increased by a median of 0.17G/l ($p<0.001$) under dupilumab (fig 1C). Five patients developed asymptomatic hypereosinophilia of more than 1 G/l, to a maximum of 1.43 G/l. FeNO was significantly decreased by -25 ppb ($p<0.0001$) while serum total IgE levels of patients without previous anti-IgE therapy decreased significantly by a median of -76 IU/ml ($p<0.0001$) (figure 1). Few side effects of dupilumab therapy were observed: three patients developed conjunctivitis, leading to discontinuation of therapy in one patient. One patient complained of headaches, one patient experienced hair loss, but both continued therapy.

Further, we classified patients into responders and non-responders using a combination of ACT-Score, pulmonary function tests and prednisolone dosage as described above. 29 patients (76%) were classified as responders of whom 24 patients (63% of total pts.) experienced a significant increase in FEV1, 12 (32% of total pts.) had a significant increase in ACT, 7 (47% of previously OCS-dependent pts.) were able to taper OCS dose more than 50%. Additionally, 10 patients (26% of total pts.) experienced a subjective response of comorbidities (table 4). In the group of non-responders (n=9), 3 patients (8%) had a significant reduction in FEV1, 2 patients (5%) had a reduction in ACT, 4 (27% of OCS-dependent pts.) needed a significant increase in OCS-dosage. One patient experienced an increase in exacerbation rate (3%) (table 4). Of note, 2 months after switching from anti-IL5R to anti-IL4R, one patient deteriorated and required a prolonged increase of prednisone dose from 5mg to 50mg/d. At reevaluation after 3 months the patient displayed improved ACT and FEV1 under 50mg/d prednisone and dupilumab (figure 2), but was classified as non-responder due to increase of prednisone, as outlined in the methods.

Patients with high FeNO (≥ 25 ppb) under previous antibody were more likely to be responders to dupilumab than patients with low FeNO (table 5 and table 6). No other associations of baseline characteristics or biomarkers were found (table 5).

Discussion:

The present study evaluates treatment response to dupilumab in a real-life cohort of severe asthmatic patients that had insufficient outcomes under a previous antibody therapy. We demonstrated that the majority of patients in this cohort improved when switched from anti-IgE or anti-IL5/IL5R α - to an IL4 R α - strategy. After 3 to 6 months of dupilumab, responders exhibited better asthma control, improvements in lung function, reduced exacerbations, response of comorbidities, and reduced T2-biomarkers FeNO and IgE.

Clinical characteristics did not differ significantly between responders and non-responders to dupilumab. However, our data indicates that high FeNO might be a predictor of response to dupilumab. This is in line with RCTs of dupilumab therapy that have shown a response in patients with FeNO ≥ 25 ppb as opposed to patients with FeNO < 25 ppb (16). However, it should be noted that the EMA prescription criteria for dupilumab require at least one elevated biomarker FeNO ≥ 25 ppb or eosinophils $> 150/\mu\text{l}$, and thus the number of patients with low FeNO of < 25 ppb in this study was small.

Targeted anti-IgE and anti-IL5/IL5R α -therapies have revolutionized the treatment of severe asthmatics. Yet, prediction of a therapeutic response to a certain biologic remains challenging, as seen in a study with mepolizumab, in which around one quarter of patients with the

indication for an anti-IL5 antibody did not show sufficient response to therapy (10). It should be noted that insufficient outcome in this study does not mean no response: patients had a benefit from the previous biologic with 46% classified as responders but still outcome was judged insufficient i.a. because asthma control was still poor or prednisone could not be tapered off completely.

If response to a biologic is not sufficient, current GINA report suggests switching to a different type 2-targeted therapy (21). However, data to support this approach is scarce. Importantly, for patients that remain uncontrolled during biological therapy, reliable predictors for a successful switch towards other antibodies have not been defined so far. Here, we provide first data showing a switch to dupilumab is effective in patients with insufficient outcomes under previous biologic.

Interestingly, our cohort of uncontrolled, severe asthmatics displayed increased T2-biomarkers despite maximum asthma therapy including anti-IgE or anti-IL5/IL5R α -antibodies: blood eosinophils were increased during anti-IgE therapy, total serum IgE was increased in patients during anti-IL5/R α - therapies and FeNO was increased in the overall cohort. A complicating factor for biomarker analysis during treatment is their alteration by biologics; e.g. total serum IgE as measured by standard assays increases during omalizumab due to the formation of IgE-omalizumab complexes (23), while the more relevant marker free serum IgE cannot be measured in routine. Further, blood eosinophil counts are usually suppressed during anti-IL5/IL5R α , but this may not always reflect the situation in the airways (24). However, anti-IgE and anti-IL5/IL5R α -treatment do not affect FeNO values and thus this marker reflects IL13-signaling even during these biological therapies (25, 26). We found that increased FeNO under previous antibody was associated to a response to dupilumab. Therefore, we suggest taking FeNO values into account in patients with insufficient outcome under biologics when switching is considered.

Other predictors of response could not be identified. However, it is noticeable, that about $\frac{3}{4}$ of the patients in this cohort had any nasal comorbidity and nearly half had nasal polyps. This percentage is higher than what is found in cohorts of recent RCTs in severe asthma (around 20% CRSwNP) (17), but similar to numbers reported from the Italian registry for severe asthma (>40% CRSwNP) (27). In that registry a higher number of exacerbations and higher OCS use was found in patients with nasal polyps (27). It is possible that patients with severe asthma and CRSwNP are more frequently among those with insufficient outcomes, even under biologics. Further, a switch to dupilumab may have been chosen more frequently in patients with nasal polyps, as it is also effective and approved for this indication (13) and

favorable outcomes for patients with nasal polyps and asthma have been reported (28, 29). In 20% of patients in this cohort a lack of response of CRSwNP was stated among the reasons for switching. Moreover, a recent study also found improvement of allergic rhinitis under dupilumab in patients with asthma and allergic rhinitis (30).

Interestingly, many patients in this cohort may be described as “mixed” phenotype at baseline with presence of allergies as well as eosinophilia. As dupilumab has pleiotropic effects on type-2 inflammation acting on eosinophils as well as reducing IgE production and FeNO, such “mixed” phenotype might be a characteristic favoring dupilumab that needs further study.

During dupilumab, we observed a reduction of FeNO and total serum IgE, but rising eosinophil levels similar to other studies (13, 19). In phase III trials of dupilumab in asthma, transient hypereosinophilia was observed in 4% and 14% of patients, respectively. This increase was rarely associated with clinical symptoms and led to the discontinuation of the drug in only a very few cases (13, 19). Increasing eosinophil levels during dupilumab were observed in all but one patient of our cohort, however, the previous discontinuation of anti-IL5/antiIL5R α -antibodies may also have contributed to this phenomenon. It is hypothesized that dupilumab blocks the transition of eosinophils from bloodstream into tissues, and hypereosinophilia therefore remains mostly asymptomatic and transient (31).

In the phase 3 Liberty Asthma Quest trial, Castro et al. showed that dupilumab improved lung function in moderate-to-severe asthma with an FEV1-increase of around 350ml, FVC-increase of around 330ml and MEF25-75 increase of 0,36 l/s after 3 months of therapy. These improvements were greater when only a specific subset of patients with higher FeNO and/or higher eosinophil levels was analyzed (17).

Our study demonstrated significant improvement of lung function changes during dupilumab, with marked increases in FEV1, FVC, MEF25-75 and reduction of RV. Remarkably, these improvements are in the range of the Liberty Asthma Quest trial of dupilumab, even though we used status under previous biologic as comparator. This might indicate that severe asthmatics in the present cohort were not *per se* less responsive to targeted therapy, but suggests that subphenotypes of severe T2 high asthma with different main pathophysiologic drivers may exist that could cause differential treatment responses to biologics.

We recognize the limitations of our study with a retrospective design and a moderate cohort size of 38 patients. Further, the timeframe from initiation of dupilumab therapy to reevaluation after 3-6 months is short, which renders analysis of exacerbations prone to error.

Finally, it should be noted that this study does not aim to compare different biologics, but to provide data for the practical approach of switching antibodies if outcome is judged insufficient. With this retrospective analysis we cannot answer the important question how to choose the optimal biologic initially, as this will require prospective interventional trials comparing different treatments in the future.

Altogether, our data indicates that dupilumab can be a safe and effective treatment option for severe asthmatic patients with insufficient outcome despite other biological therapies. As differential predictive biomarkers and comparative trials are currently lacking, therapeutic trials of antibody switching are justified in these patients.

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Tables and Figures

Figure legends:

Figure 1: Lung function parameters (A), clinical parameters (B) and biomarkers (C) before antibody therapy, during previous antibody therapy, and after 3-6 months of dupilumab therapy. All graphs in (A) and ACT from (B) display mean $\pm$ -SD; rest of (B) + (C) median $\pm$ -IQR. Statistics of previous antibody versus dupilumab (A) + ACT by paired t-test and rest of (B) + (C) by Wilcoxon matched-pairs signed rank test: * $p<0.05$, ** $p<0.01$, *** $p<0.001$, **** $p<0.0001$;

Figure 2: Individual analysis of lung function parameters (A), clinical parameters (B) and biomarkers (C) during previous antibody therapy, and after 3-6 months of dupilumab therapy. Left graph patients classified as responders (blue), right graph patients classified as responders (red). Statistics of responders comparing previous antibody versus dupilumab: (A) + ACT by paired t-test and rest of (B) + (C) by Wilcoxon matched-pairs signed rank test: * $p<0.05$, ** $p<0.01$, *** $p<0.001$, **** $p<0.0001$;

498 **Table 1: Clinical characteristics of the study population.**

Baseline characteristics of study population	n=38
Age, mean (SD) years	55 (12)
Female, n (%)	22 (58%)
Male, n (%)	16 (42%)
BMI, median (IQR) kg/m ²	25 (22-31)
Age at asthma diagnosis, median (IQR) years [#]	25 (10-47)
Time since asthma diagnosis, median (IQR), years [#]	27 (10-42)
Allergies, n (%)	29 (76%)
Polysensitization, n (%)	19 (50%)
Former smokers, n (%)	10 (26%)
Comorbidities	
ENT-comorbidities, n (%)	28 (74%)
Nasal polyposis, n (%)	18 (47%)
Allergic rhinitis, n (%)	18 (47%)
Chronic sinusitis without nasal polyps, n (%)	10 (26%)
Atopic dermatitis, n (%)	12 (32%)
Aspirin intolerance, n (%)	7 (18%)
Steroid induced side effects, n (%)	16 (42%)

499 Abbreviations: BMI body mass index, ENT ear nose throat. [#]n=36

500

Table 2: Medication, lung function and biomarkers without antibody and during previous antibody therapy.

Baseline characteristics and biomarkers before and during anti-IL-5/anti-IgE therapy		
n=38	Without antibody	During previous antibody (anti-IgE, anti-IL5)
Medication		
ICS/LABA (high), n (%)	27 (75%)*	31 (82%)
ICS/LABA (medium), n (%)	9 (25%)*	7 (18%)
LAMA, n (%)	29 (81%)*	33 (87%)
LTRA, n (%)	22 (61%)*	23 (61%)
Number of pts. with OCS, n (%)	23 (64%)*	15 (39%)
Dose of prednisolone in mg, median (IQR) in patients with baseline OCS	10 (5-15)	4 (0-10)
Previous biologic		
Mepolizumab, n (%)	-	11 (29%)
Benralizumab, n (%)	-	19 (50%)
Reslizumab, n (%)	-	2 (5%)
Omalizumab, n (%)	-	6 (16%)
Duration of previous biological therapy, median (IQR), months		10 (7-14)
Asthma Control and exacerbations		
ACT-Score, mean (SD)	12 (5) ^{§§}	14 (5) ⁺
Number of pts. with exacerbations before/ during previous antibody, n (%)	23 (60%) ⁺⁺	21 (55%)
Calculated number of annualized exacerbations during previous antibody, median (IQR)	2 (1-4)	0.8 (0.0-2.4)
Lung function		
FEV1 in l, mean (SD)	1.90 (0.70) *	1.89 (0.87)
FEV1 % predicted, mean (SD)	62% (20) *	60% (22)
FVC in l, mean (SD)	3.00 (0.89) *	3.08 (1.2)
FVC % predicted, mean (SD)	80.3% (18) *	81% (20)

RV in l, mean (SD)	3.17 (1.23) *	3.06 (0.86)
RV % predicted, mean (SD)	158% (58) *	144% (34)
TLC in l, mean (SD)	6.38 (1.37)	6.34 (1.34)
TLC % predicted, mean (SD)	107 (20)	105 (14)
FEV1/FVC	0.62 (0.12)	0.60 (0.12)
MEF25-75 in l/s, mean (SD)	1.02 (0.70) *	1.08 (0.73) *
MEF25-75 % predicted, mean (SD)	33% (29) *	32% (21) *
Reff in kPa*s/l, mean (SD)	NA	0.50 (0.35) [#]
Reff % predicted, mean (SD)	NA	163% (115) [#]
Biomarker		
FeNO in ppb, median (IQR)	52 (30-129) §	55 (29-99) ⁺
Eosinophils in G/l, median (IQR)- all pts	0.41 (0.21-0.62)	0.04 (0.00-0.18) ⁺
Eosinophils in G/l, in pts. with anti-IL5/IL5R α therapy -median (IQR) **	0.48 (0.23-0.68)	0.0 (0.0-0.13)
Eosinophils in G/l, median (IQR) in pts. with anti-IgE therapy ^{##}	0.21 (0.15-0.62)	0.2 (0.16-0.42)
IgE in IU/ml, median (IQR)- all pts	333 (53-534)	
IgE in IU/ml, in pts. with anti-IL5/IL5R α therapy -median (IQR) ⁺⁺	148 (52-496)	186 (49; 365)
IgE in IU/ml, in pts. with anti-IgE therapy -median (IQR) ^{##}	344 (55-4340)	

Abbreviations: ICS inhaled corticosteroid, LABA long-acting beta-agonist, LAMA long-acting muscarinic antagonist, LTRA leukotriene receptor antagonist, OCS oral corticosteroid, ACT asthma control test, FEV1 forced expiratory volume in 1 second, FVC forced vital capacity, RV residual volume, MEF25-75 maximum expiratory flow at 25-75% of forced vital capacity, Reff specific airway resistance, FeNO fraction of exhaled NO, IgE Immunoglobulin E. [#]n=37, *n=36, ⁺n=35; ** n=29, ^{##}n=6, ⁺⁺n=27; §n=24, §§n=19 .

Table 3: Indications for switch to dupilumab.

Indication for switch to dupilumab	n=38
Insufficient subjective response, n (%)	32 (84%)
Insufficient reduction in exacerbations	18 (47%)
Insufficient change in lung function	26 (68%)
Insufficient response of comorbidities	11 (29%)

Insufficient change in symptoms of nasal polyposis	8 (21%)
Insufficient reduction of OCS	12 (32%)
Persistent eosinophilia	5 (13%)
Persistent allergic symptoms	2 (5%)
Side effect of previous antibody	1 (3%)

Abbreviations: OCS oral corticosteroid. n=38

Table 4: Classification of responders and non-responders to dupilumab.

Classification of response to dupilumab	
	n=38
Responder group	n=29 (76%)
ACT-increase (≥ 3 points), n (% of all patients)	12 (32%)
FEV1-increase (≥ 150ml), n (% of all patients)	24 (63%)
OCS-reduction ($\geq 50\%$), n (% of OCS dep. patients)	7 (47%)
Response of comorbidities, n (% of all patients)	10 (26%)
Non-responder group	n=9 (24%)
ACT-reduction (≥ 3 points), n (% of all patients)	2 (5%)
FEV1-reduction (≥ 150ml), n (% of all patients)	3 (8%)
OCS-increase ($> 50\%$), n (% of OCS dep. patients)	4 (27%)
Increase in exacerbations (% of all patients)	1 (3%)

Response to dupilumab was defined as at least one positive response criterion without significant deterioration in any other criterion: 1) Increase in FEV1 of at least 150ml. 2) Increase in ACT of at least 3 points. 3) Reduction of OCS dosage of at least 50%. Significant deterioration was defined as 1) loss in FEV1 of 150ml or more, 2) decrease of ACT of 3 points or more, 3) every increase of OCS dose more than two weeks, 4) increase in exacerbations.

Table 5: Contingency table analyses of clinical characteristic, biomarkers during previous therapy and response to dupilumab.

	P
Clinical characteristics	
Age [*]	0.286
Sex [*]	0.254
Early onset asthma (<12y) (Y/N) [*]	1.0
ENT comorbidities (Y/N) [*]	0.56
OCS therapy during previous therapy (Y/N) [*]	1.0
Biomarkers during previous therapy	
FeNO (high/low) [°]	0.015
Eosinophil count (high/low) [#]	0.121
IgE (high/low) [°]	0.635

“FeNO high” ≥ 25 ppb, “eosinophil count high” ≥ 0.15 G/l, “IgE high” ≥ 100 IU/ml. ^{*}n=38 [#]n=37, [°]n=35.

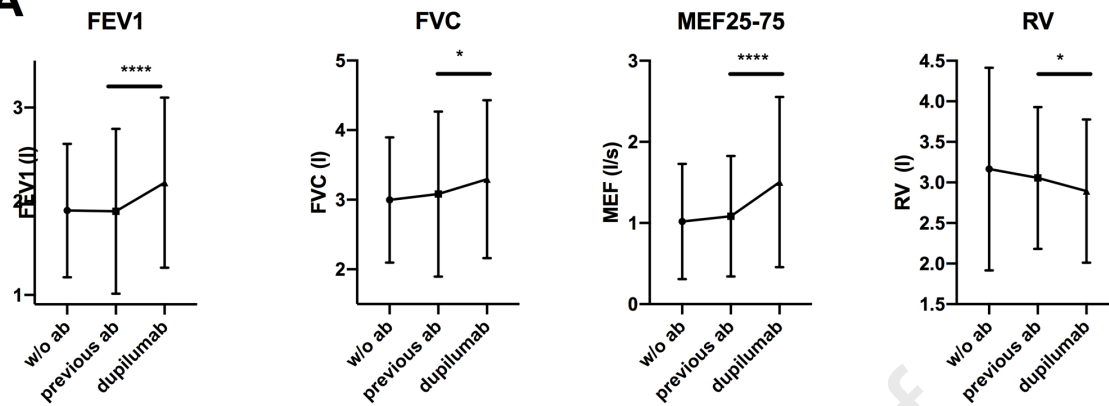
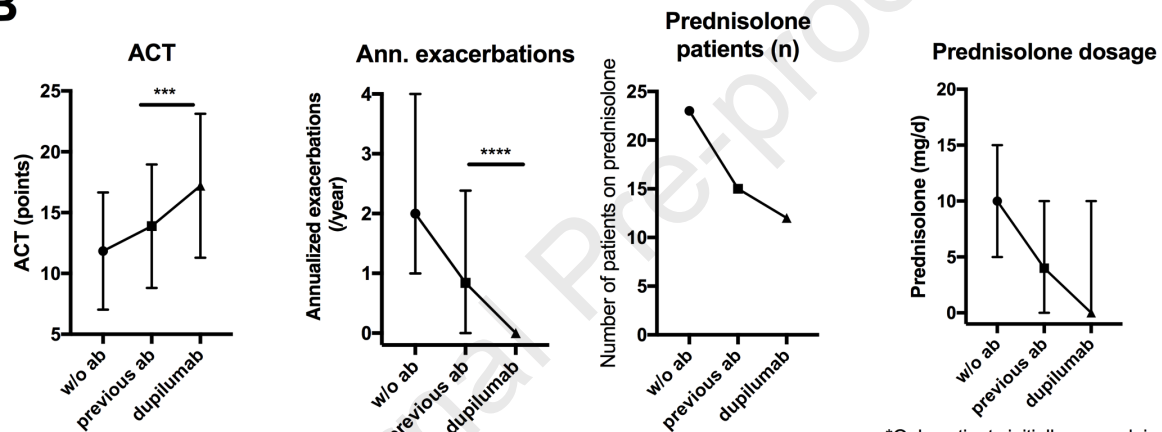
Statistics: for age: Chi-Square-Test; for sex, early onset asthma, late onset asthma, OCS therapy:

Fishers-Exact test (two-sided); for biomarkers and ENT comorbidities: Fishers-Exact test (one-sided)

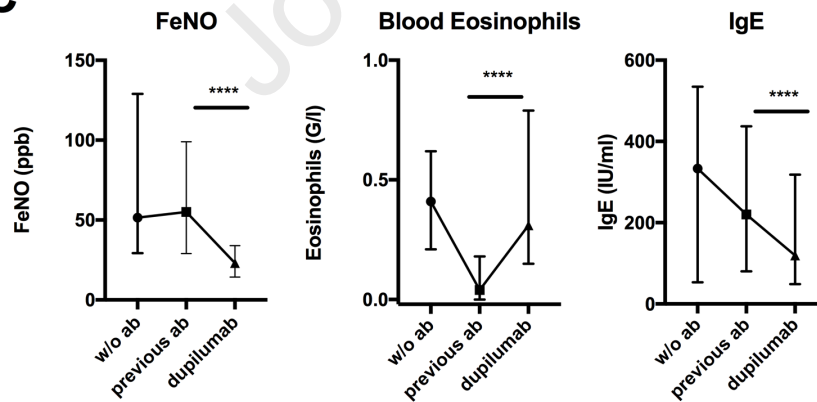
Table 6: Contingency Table of Responder status and FeNO category

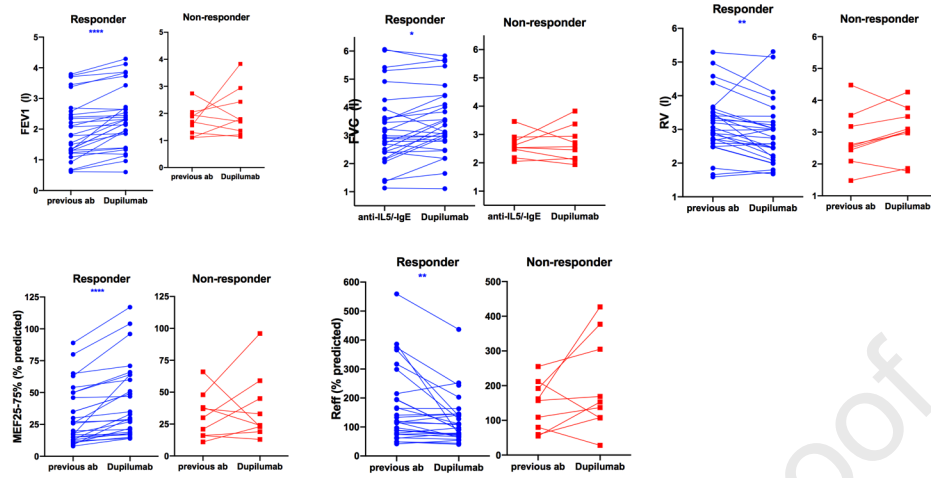
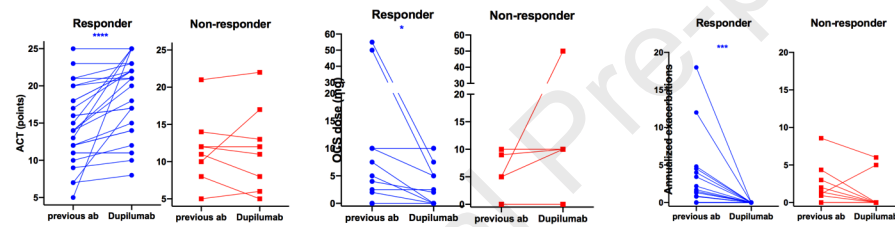
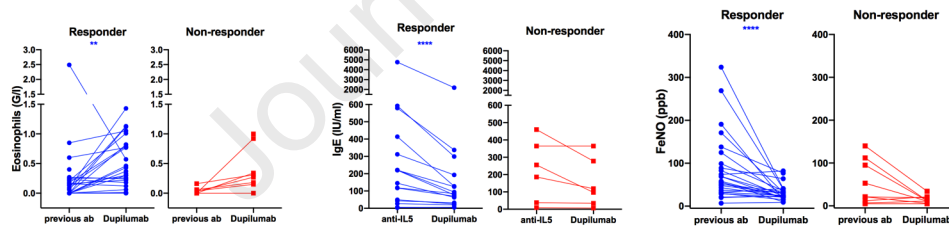
	Non-Responder	Responder	Total
FeNO ≥ 25 ppb	4	23	27
FeNO < 25ppb	5	3	8
Total	9	26	35

n=35; in 3 patients FeNO under previous ab was not available.

A**B**

*Only patients initially on prednisolone
n=23

C

A**B****C**

Repository Figure Legends:

Figure E1: Patients with anti-IL5 as previous antibody (n=32). Lung function parameters (A), clinical parameters (B) and biomarkers (C) before antibody therapy, during previous antibody therapy, and after 3-6 months of dupilumab therapy. All graphs in (A) and ACT from (B) display mean $\pm$ -SD; rest of (B) + (C) median $\pm$ -IQR. Statistics of previous antibody versus dupilumab (A) + ACT by paired t-test and rest of (B) + (C) by Wilcoxon matched-pairs signed rank test: * $p<0.05$, ** $p<0.01$, *** $p<0.001$, **** $p<0.0001$;

Figure E2: Patients with anti-IgE as previous antibody (n=6) Lung function parameters (A), clinical parameters (B) and biomarkers (C) before antibody therapy, during previous antibody therapy, and after 3-6 months of dupilumab therapy. All graphs in (A) and ACT from (B) display mean $\pm$ -SD; rest of (B) + (C) median $\pm$ -IQR. Statistics of previous antibody versus dupilumab (A) + ACT by paired t-test and rest of (B) + (C) by Wilcoxon matched-pairs signed rank test: * $p<0.05$, ** $p<0.01$, *** $p<0.001$, **** $p<0.0001$;