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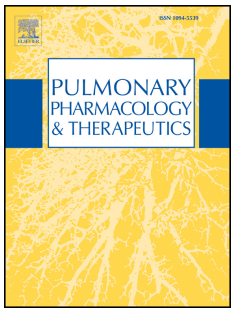

Mepolizumab effectiveness on small airway obstruction, corticosteroid sparing and maintenance therapy step-down in real life

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Original article

Mepolizumab effectiveness on small airway obstruction, corticosteroid sparing and maintenance therapy step-down in real life.

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Running Head: Mepolizumab in real-life

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Abstract

Background: Mepolizumab (MEP) has been recently introduced to treat severe eosinophilic asthma. Trials have demonstrated a significant effectiveness in this phenotype. We evaluated MEP efficacy on lung function, symptoms, asthma exacerbations, biologic markers, steroid dependence and controller treatment level in real-life.

Methods: We retrospectively analyzed 134 severe asthmatics (61 males; mean age 58.3±11; mean FEV_1%:72±21), treated with MEP for at least 6 months (mean duration:10.9±3.7 months)

Results: FEV_1% improved significantly after MEP. Mean FEF_{25-75} also increased from 37.4±25.4% to 47.2±27.2% ($p<0.0001$). Mean baseline blood eosinophil level was 712±731/µL (8.4±5.2%) decreasing to 151±384/µL (1.6±1.6%) ($p<0.0001$), FENO levels decreased likewise. MEP treatment also led to a significant ACT improvement (mean pre:14.2±4.4; mean post:20.5±28) and exacerbations significantly fell from 3.8±1.9 to 0.8±1.1 ($p<0.0001$). 74% of patients were steroid-dependent before MEP. 45.4% and 46.4% of them showed a suspension and dose reduction respectively ($p < .0001$). A significant number reduced also ICS doses. Only 67% of subjects used SABA as needed before MEP, falling to 20% after MEP. About 50% of patients highlighted a maintenance therapy step-down. Subjects showing an omalizumab treatment failure before MEP had a similar positive response when compared with omalizumab untreated patients.

Conclusion: In real-life, MEP improved significantly all outcomes even small airway obstruction, suggesting its possible role also in distal lung region treatment. Furthermore, it demonstrated its high effectiveness in OC/ICS-sparing, in reducing SABA as needed and in stepping-down maintenance therapy. MEP is a valid alternative for patients with previous omalizumab treatment failure.

1. Introduction

According to ATS/ERS severe asthma is characterized by poor symptom control and frequent exacerbations despite the use of high doses of inhaled corticosteroids (ICS), long acting bronchodilators and anti-leukotrienes [1]. In Italy, severe asthma phenotype affects about 5.6% of all asthmatics [2]. Severe asthma burdens for more than 50% of overall direct and indirect costs concerning the disease [3,4]. Fortunately, some biological drugs (anti-IgE or anti-IL5/anti-IL5R) that can significantly improve treating severe asthma are available today. Anti-IL5/IL5R monoclonal antibodies are effective in controlling eosinophilic airway inflammation that characterizes most severe asthma patients. Based on blood eosinophil cut-offs greater than or equal to 150/300 cells/µL, 61%/41% respectively of all severe asthmatics had an eosinophilic phenotype [5]. Mepolizumab (MEP) has been available in Italy for about 2 years for eosinophilic severe asthma as an add-on therapy in patients with still uncontrolled disease despite a maximal treatment as required by step 5 of GINA guidelines [6]. MEP is an IgG1/k class humanized monoclonal antibody that is able to block circulating IL-5 which is responsible for eosinophil development, maturation and survival. Thus MEP, by blocking IL-5, can reduce the eosinophil count with consequent improvement in asthma outcomes. In fact, different MEP trials have clearly demonstrated, through a meaningful lowering of blood eosinophils, to be able to reduce asthma exacerbations, to have a significant glucocorticoid-sparing effect and to improve asthma symptom control [7-10]. On the contrary, there are only few MEP effect data in real-life settings [11-16]. However, all studies confirmed MEP effectiveness. Nevertheless, considering that approximately only 300 asthmatics have been studied in real-life to date, we retrospectively evaluated MEP outcomes in a group of severe asthmatics in order to add further data concerning its use. In particular, we analyzed not only MEP clinical and biological effects but also possible improvements on small

airway obstruction and on the reduction of oral/inhaled corticosteroids, SABA use and other controller treatments.

2. Materials and Methods

This retrospective study considered 134 severe asthmatics who had referred to twenty Italian severe asthma centers and who had been treated with MEP for at least 6 months between 01st May 2017 and 31st December 2018. All centers shared a common database reporting the clinical, functional and biological characteristics of the enrolled patients. All subjects had a diagnosis of severe asthma fulfilling all the diagnostic criteria established by guidelines [1]. They had been poorly controlled even while using high ICS doses, oral corticosteroids (OC), long-acting bronchodilators and anti-leukotrienes (montelukast) which made it necessary to add MEP, as recommended by steps 5 of GINA asthma guidelines [6]. All patients had to be adherent to inhaled treatments and had to use devices correctly. MEP was prescribed to patients that had a peripheral blood eosinophil count above 300/µL in at least one occasion during the previous year and more than 150/µL before the first MEP injection. All the included subjects received 100 mg MEP subcutaneously every 4 weeks. The study was undertaken in accordance with the Helsinki Declaration and was approved by the Local Ethical Committee of Pisa University Hospital, within the context of an observational multi-centre project on severe asthma in Italy (n. 1245/2016). Informed consent was obtained by each patient for the use of personal data. Information concerning allergic sensitization (*Dermatofagoides pteronissinus and D. farinae, Grass mix, Parietaria, Olea europaea, Cupressus sempervirens, Betula pendula, Alternaria tenuis, Aspergillus f. and dog-cat dander*), IgE serum values, blood eosinophil counts, the presence of rhinitis, sinusitis, nasal polyposis, and/or other comorbidities (systemic hypertension, chronic heart disease, diabetes, osteoporosis, gastro-esophageal reflux, COPD, obesity), smoking habits and body mass index (BMI) were required for each patient. Furthermore, asthma onset age and period of

treatment were also recorded. Lung function variables (FEV_1%, FEF_{25-75}%), Asthma Control Test (ACT), blood eosinophil counts, fractional exhaled nitric oxide (FENO) and number of moderate/severe exacerbations were evaluated at the moment of MEP prescription and at the end of each patient's treatment period. ICS doses, oral corticosteroids, SABA use as rescue medication, montelukast and other inhaled drugs taken, plus their step-downs/step-ups, were also considered. Moderate/severe exacerbations, requiring systemic corticosteroids for at least 3 days, were taken into account as well. The daily dosage of beclomethasone dipropionate or the equivalent dose of other corticosteroids used (fluticasone budesonide or others) were expressed as low (≤500 mcg), medium (500–1000 mcg) or high (≥1000 mcg), according to GINA classification of ICS dose equivalence [6]. SABA use (number of times a week) in the month before starting MEP and during the 30 days before the end of each patient's MEP treatment period was also considered. Besides, we analyzed treatment responses in subjects that had taken Omalizumab before MEP was prescribed and compared them with the outcomes observed in the others.

2.1. Statistical analysis

Continuous variables were expressed as means and standard deviations (SD). Categorical variables were considered as number of cases and percentages. Comparisons of continuous variables were performed by using the paired t-test or the Wilcoxon signed-rank test in order to assess the difference between “before” and “after” treatment. Categorical variable frequencies were compared by chi-square test or Fisher's exact test, as appropriate. Comparisons of various outcome changes obtained after MEP (post-treatment – pre-treatment) in patients that had taken Omalizumab before anti-IL5 and in those that had not taken anti-IgE were done by using Mann-Whitney U test.

3. Results

This study included 134 severe asthmatic subjects (61 males - 45.5%; mean age 58.3±11; mean time of treatment 10.9±3.7 months; smokers 6 – 4.5%). All patients' baseline characteristics are reported In table 1. Lung function after MEP improved significantly (fig.1). Mean FEV_1 before MEP was 72±21% (2±0.8 L), whereas it was 78±20% (2.21±0.8 L) after treatment (fig.1/A; p<0.0001). Mean FEF_{25-75} was 37.4±25.4% (1.4±1.1 L/sec) before MEP and 47.2±27.2% (1.61±1L/sec) at the end of treatment (fig.1/B; p<0.0001). Markers of asthma control and of eosinophilic inflammation were significantly reduced by MEP. Mean baseline blood eosinophil level was 712±731/µL (8.4±5.2%) decreasing to 151±384/µL (1.6±1.6%) after MEP (fig.2/A; p<0.0001). Mean FENO level likewise decreased from 54.1±32.8 to 41.5±31.9 ppb (fig.2/B; p<0.0001). MEP treatment also led to a significant improvement in ACT (mean pre: 14.2±4.4; mean post: 20.5±28) and to an important exacerbation reduction which dropped from 3.8±1.9 before MEP to 0.8±1.1 after treatment (fig.2/C and D; p<0.0001). Overall, an ICS dose reduction was observed after almost one year of MEP treatment. In fact, 14.9, 47.8 and 37.3% of all patients took low, medium and high doses of ICS respectively before treatment, whereas percentages changed to 25.4, 58.2 and 15.7% (fig.3/A; p<0.022) after MEP. Patients who were taking low/medium doses of ICS before MEP were all prescribed oral corticosteroids, consequently, their doctors decided to reduce the previous high ICS doses in order to prevent adverse effects. Subjects that took long-term oral corticosteroids were 74% before treatment, decreasing to 43% after approximately one year of MEP (fig.3/B; p<0.0001). In particular, 45.4% and 46.4% of patients that took OC showed a suspension and a dose reduction of OC respectively (fig.4/A). One month before beginning MEP treatment, 67.7% of subjects had taken SABA, whereas only 20.6% of them had used SABA one month before the end of each patient's MEP therapy (fig.3/C; p<0.0001). LABA use remained unchanged during MEP treatment. Although not significant, percentage reductions of patients that took Tiotropium (from 57.7% to 47.5%) and Montelukast (from 43.6% to 32.5%) were observed during anti-IL5

treatment (fig.3/D,E and F). On the whole, we observed a step down of maintenance treatment in 53.4% of subjects (fig.4/B).

When considering Omalizumab non-responders who had taken the anti-IgE before Mepolizumab (21 patients) and compared them with those that had not taken any biologics before Mepolizumab (82 subjects) we found similar results in changes (post – pre) of FEV_1%, FEF_{25-75}%, blood eosinophils and FENO. The percentages of subjects that had a step-down of maintenance treatment or that reduced/stopped OC (table 2) were also the same. Only ACT improvement was higher in subjects untreated with Omalizumab prior to MEP (7±4.5) in comparison with subjects treated with anti-IgE before Mepolizumb (4.7±4; p=0.031; table 2).

4. Discussion

This retrospective study highlighted, similarly to others [11-16], that MEP can lead to an improvement in all outcomes considered (lung function, biological markers, symptoms, OC/ICS-sparing and therapy level maintenance) in severe eosinophilic asthma. In agreement with other studies, [14,16] the improvement of various outcomes (FEV_1%, and exacerbations) after MEP was greater than the one encountered in the main clinical trials [7]. In fact, we found a FEV_1 increase of about 200 ml and a reduction of exacerbations of approximately 80% in real-life versus a FEV_1 variation of 98 ml and an exacerbation decrease rate of 53% after MEP in clinical trials [7]. These results suggest an excellent effectiveness of anti-interleukin-5 therapy in patients with poorer clinical characteristics (older age and comorbidities) compared to those described in regulatory trials.

We also observed a significant improvement in FEF_{25-75}% as expression of a possible MEP effect on small airways. The forced expiratory flow at 25–75% of FVC (FEF25–75%) is the spirometric variable most commonly cited as an indicator of small airway obstruction in literature [17]. Such

small airway impairment, as assessed with FEF_{25-75}, might contribute to long-term persistent asthma and the subsequent risk for poor asthma outcomes**,** independently of large airway status [18]. According to recent articles, MEP can significantly improve small airways in severe eosinophilic asthma measured with multiple breath nitrogen washout [19]. The improvement in small airway function is associated with asthma control and may be a significant contributor to therapeutic response [19]. Biologics, in this case MEP, might be the most targeted therapies to treat distal lung regions.

Regarding asthma symptoms, MEP produced a significant ACT score improvement (14.2–20.5; $p<0.0001$). ACT variations were higher than the accepted minimal clinically important differences of 3 points in real life [20], confirming an excellent MEP effectiveness on symptoms.

Obviously, such effectiveness is related to a significant eosinophil reduction that was about 80% in our study, a value higher than the one obtained in MENSA trial [7]. FENO, an airway eosinophilic inflammation marker, also decreased significantly after MEP. Such result had already been found by other authors [14]. Eosinophilic asthma phenotype is characterized by high eosinophil levels in induced sputum and peripheral blood and is associated with more frequent symptoms/exacerbations and a greater airflow limitation [21,22]. Failure to reduce eosinophils, even after maximal therapy, could be associated with unstable asthma and with a reduced clinical and functional response to treatment [23,24]. Therefore, the reduction of eosinophilic airway inflammation is the target that must be sought for the treatment of eosinophilic asthma phenotype. Mepolizumab, significantly reducing eosinophils, is the drug of choice in eosinophilic asthma refractory to conventional treatment.

Our study also showed that MEP led to a suspension/reduction of oral corticosteroids in about 90% of subjects treated with OC. Such result is slightly higher when compared to other studies [16] that found that 68% of patients stopped OC treatment or received a >50% dose reduction. Other

studies have also described this effect with a reduction of 50% of the OC dose, according to some researchers [9], and 80% of the OC dose intake, according to others [14]. Furthermore, our study highlighted that there was an ICS dose reduction in about 20% of patients. Therefore, MEP demonstrated to be highly effective OC/ICS-sparing in real life with beneficial consequences also on corticosteroid adverse effects. In the future, chronic and acute OC use in asthma may be replaced by biological agents targeting eosinophilic airway inflammation more specifically and safely [25].

We also observed that about 20% of patients stopped Tiotropium and Montelukast approximately after one year of MEP therapy. In addition, the use of SABA as needed before MEP was used by 67% of subjects**,** falling to 20% after MEP treatment. Totally**,** we observed a step-down of maintenance treatment in about 50% of patients. A lower use of controller medications has been obtained also with Omalizumab**,** above all after long-term treatments [26]. This reduced use of controller drugs, when effected on a large number of patients, might have pharmacoeconomic repercussions [27].

Another interesting aspect was that poor Omalizumab responders (who used Omalizumab prior to MEP) had a response similar to the one in subjects treated directly with anti-IL5, except for ACT which showed a lower increase in patients previously treated with Omalizumab. Anti-IgE non responders should be considered more resistant to treatments. However, Mepolizumab, as it has already been clearly demonstrated by other trials [28-31], confirms to be an excellent alternative in severe allergic asthmatics who are poorly responsive to Omalizumab even in real life .

5. Conclusion

MEP proved to be effective in improving lung function, symptoms and in reducing exacerbations in real-life settings. It has been shown to be particularly beneficial even on small airway obstruction,

suggesting that it might be a targeted biologic to treat distal lung regions. Furthermore, MEP demonstrated to be highly effective in OC/ICS-sparing, in reducing the use of SABA as needed and overall it may also lead to a maintenance therapy step-down. MEP is also useful for patients with previous Omalizumab treatment failure.

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Conflict of interest

On behalf of all authors, the corresponding author states that there is no conflict of interest.

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Legend of figures

Table 1. Baseline characteristics of 134 eosinophilic severe asthmatics

Comorbidities considered were: gastro-esophageal reflux disease, hypertension, chronic heart disease, diabetes, osteoporosis, obesity and COPD

Figure 1. FEV_1% (A) and FEF_{25-75}% measured before (pre-treatment) and after (post-treatment) about 11 months of Mepolizumab therapy.

Figure 2. Blood eosinophils counts (A), FENO values (B), ACT rate (C) and number of exacerbations (D) measured before (pre-treatment) and after (post-treatment) about 11 months of Mepolizumab therapy.

Figure 3. Percentages of patients that took low/medium/high ICS doses (A), oral corticosteroids (B), SABA as needed (C), and various controller medications (LABA, Tiotropium an Montelukast) (D, E and F) measured before (pre-treatment) and after (post-treatment) about 11 months of Mepolizumab therapy.

Figure 4. Percentages of patients that reduced the doses of oral corticosteroids or stopped them (A) and whose level of maintenance therapy was modified after about 11 months of Mepolizumab treatment

Table 2. Comparisons of various outcome changes obtained after about 11 months of Mepolizumab treatment (post-values – pre-values) between non responders to previous Omalizumab therapy and subjects that had never been treated with Omalizumab before Mepolizumab.

Differences were calculated by subtracting post from pre-values.

Table 1

Age	58.3±11
Males	61 (45.5%)
Months of Mepolizumab treatment	10.9±3.7
BMI	26.5±4.3
Smokers	6 (4.5%)
Ex-Smokers	43 (32.1%)
Age of asthma onset (yrs)	36.5±16.9]
Total serum IgE UI/ml	310.6±430.3
FEV_1% pre-Mepolizumab	72±21
FEV_1/FVC pre-Mepolizumab	66±13
House dust mite	60 (44.8%)
Pollens	48 (36%)
Moulds	9 (8.1%)
Cat/dog dander	18 (13.4%)
Mono-sensitized (to 1 allergen)	36 (26.8%)
Poly-sensitized (≥2 allergens)	40 (29.9%)
N° of subjects with rhinitis (%)	78 (59%)
N° of subjects with sinusitis (%)	63 (47.7%)
N° of subjects with nasal polyposis (%)	69 (52.3%)
N° of subjects with 0 comorbidity (%)	55 (42.3%)
N° of subjects with ≥1 comorbidities (%)	75 (57.7%)

Table 2

	Previous failure with Omalizumab treatment (21 subjects)	**No previous Omalizumab treatment (82 subjects)**	**p**
Δ FEV_1 %	7.5±15	6.5±17	0.489
Δ FEF_{25-75}%	8.5±16.5	11.2±27.1	0.763
Δ Blood eosimophils	-901.8±990.9	-537.5±342.1	0.597
Δ FENO	-10.9±22.3	-6.35±52.2	0.881
ACT	4.7±4	7±4.5	**0.031**
Exacerbations	-3.1±1.9	-3.3±1.7	0.629
Level of therapy			
Unchanged	12 (57.2%)	36 (43.9%)	0.256
Step-up	0	8 (9.8%)	
Step-down	9 (42.8%)	38 (46.3%)	
Oral corticosteroids			
Unchanged	2 (9.5%)	5 (6.1%)	0.550
Reduced	10 (47.7%)	31 (37.8%)	
Stopped	7 (33.3%)	38 (46.3%)	
Never used	2 (9.5%)	8 (9.8%)	

Figure 1

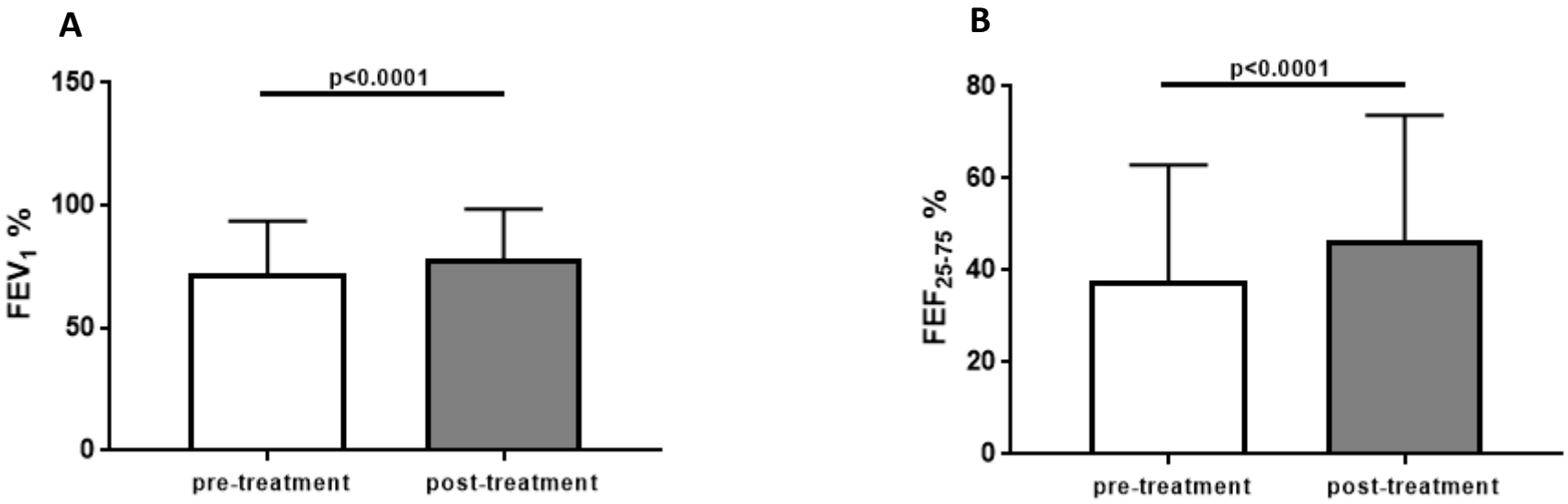

A
p<0.0001
150
100
50
0
FEV1 %
pre-treatment
post-treatment
B
p<0.0001
80
60
40
20
0
FEF25-75 %
pre-treatment
post-treatment

Figure 2

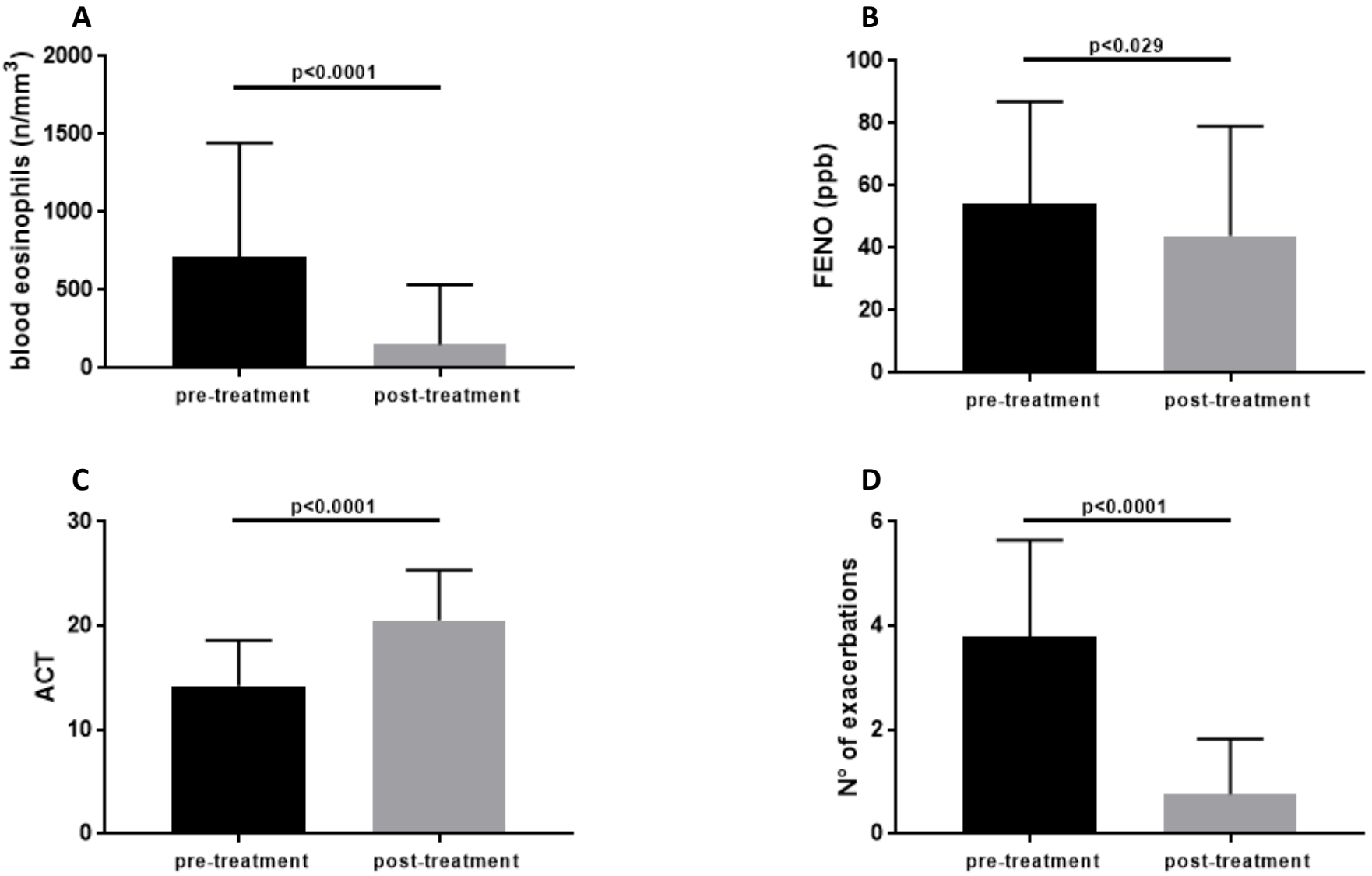

A
blood eosinophils (n/mm3)
2000
1500
1000
500
0
p<0.0001
pre-treatment
post-treatment
B
FENO (ppb)
100
80
60
40
20
0
p<0.029
pre-treatment
post-treatment
C
ACT
30
20
10
0
p<0.0001
pre-treatment
post-treatment
D
N° of exacerbations
6
4
2
0
p<0.0001
pre-treatment
post-treatment

Figure 3

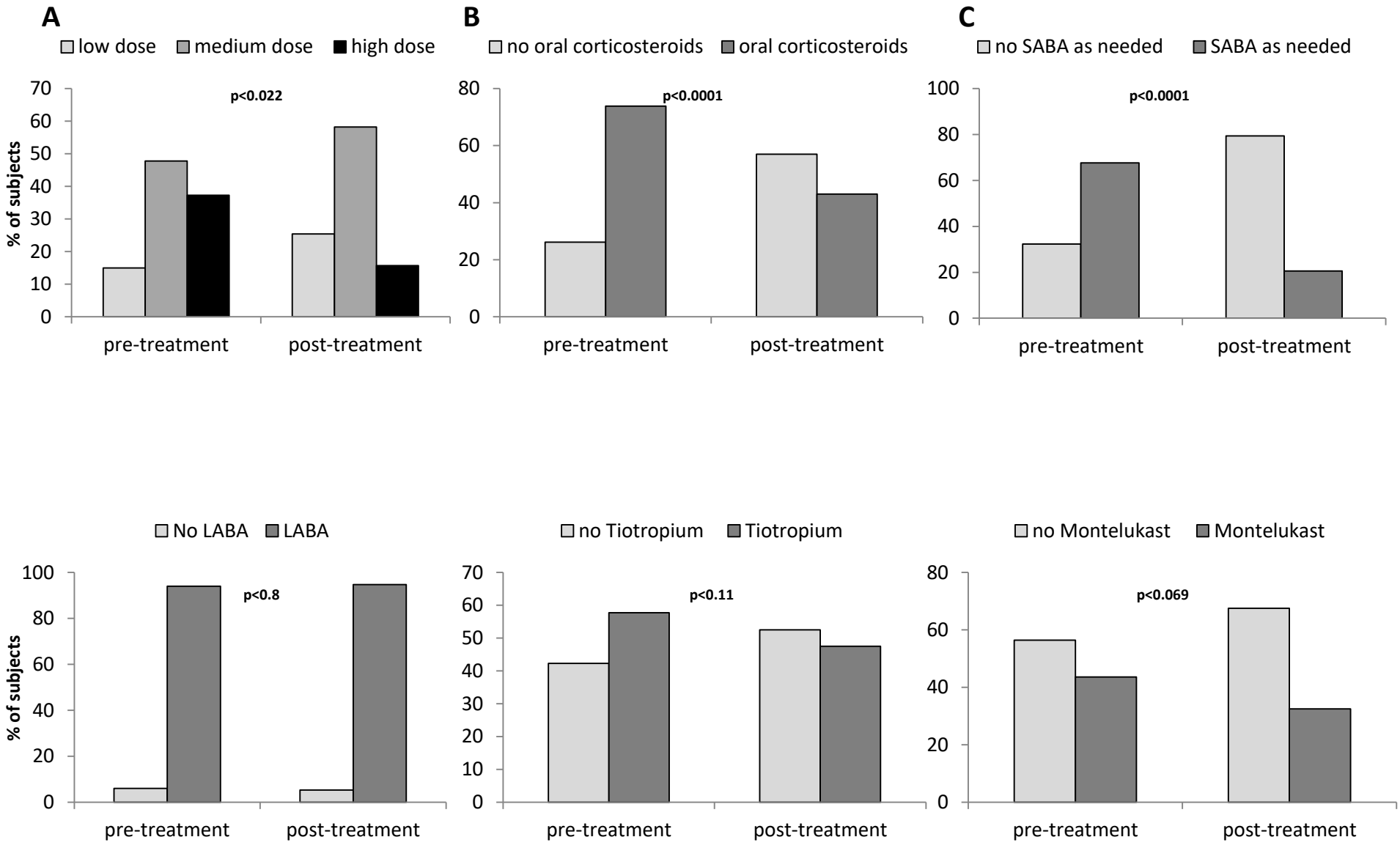
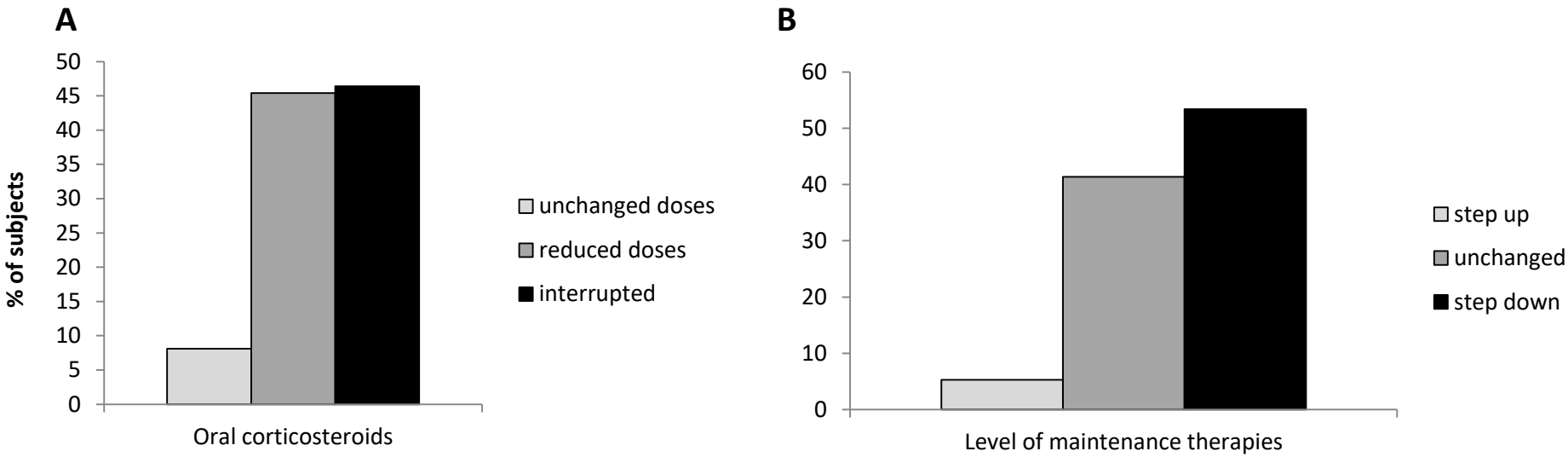

A
low dose
medium dose
high dose
% of subjects
p<0.022
pre-treatment
post-treatment
B
no oral corticosteroids
oral corticosteroids
p<0.0001
pre-treatment
post-treatment
C
no SABA as needed
SABA as needed
p<0.0001
pre-treatment
post-treatment
No LABA
LABA
% of subjects
p<0.8
pre-treatment
post-treatment
no Tiotropium
Tiotropium
p<0.11
pre-treatment
post-treatment
no Montelukast
Montelukast
p<0.069
pre-treatment
post-treatment

Figure 4


A
50
45
40
35
30
25
20
15
10
5
0
% of subjects
Oral corticosteroids
unchanged doses
reduced doses
interrupted
B
60
50
40
30
20
10
0
Level of maintenance therapies
step up
unchanged
step down