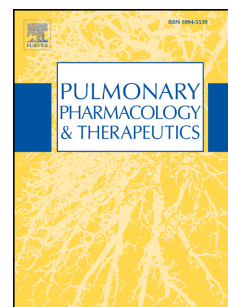


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2nd REVISION

One year of mepolizumab. Efficacy and safety in real-life in Italy.

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42

43 **ABSTRACT:**

44 **Background:** Severe asthma is a disease with a heavy socio-economic burden and a relevant
45 impact on the life of patients. Mepolizumab (MEP) was recently introduced in practice. The
46 previous data were favourable as efficacy and safety are concerned. Nowadays, we can report the
47 clinical data after more than one year of use of MEP in the real-life setting.

48 **Objective**

49 To evaluate the efficacy and safety of MEP in a real life framework, mainly concerning asthma
50 exacerbations, steroid dependence, effects on respiratory function and adverse events.

51 **Methods**

52 This retrospective analysis was performed on 138 patients, treated with MEP for at least 12 months,
53 and referred to eleven severe asthma clinics in Italy. All patients met the criteria for severe
54 uncontrolled asthma according to ATS/ERS guidelines and prescribing MEP conditions according
55 to the Italian Drug Agency (AIFA).

56 **Results**

57 We could observe 138 patients (78 female, age 58 ± 10 years). The average age of onset of asthma
58 was 34 ± 16 years. The blood eosinophil count decreased from $822 \pm 491/\mu\text{L}$ at baseline to 117 ± 96
59 $/\mu\text{L}$ ($p < .0001$) after 12 months of therapy. Exacerbations decreased from 3.8/year to 0.7/year (-
60 81%; $p < .0001$). Steroid-dependent patients before MEP (80%) with a daily dose of 10.1 ± 9.4 mg
61 prednisone decrease at 28% after 12 months with a mean of 2.0 ± 4.2 mg/day ($p < .0001$). The
62 occurrence of adverse events was overall low.

63 **Conclusions & Clinical relevance**

64 In this real-life setting, MEP confirmed its efficacy and safety profile, already shown in clinical
65 trials. This was apparent concerning exacerbation rate, systemic steroids intake and safety.

66

67 **KEYWORDS**

68 Asthma, eosinophils, biologics, quality of life, severe asthma, mepolizumab, real life, IL-5, OCS,
69 exacerbations, safety.

70 **ABBREVIATIONS**

71 MEP: Mepolizumab

72 OCS: Oral corticosteroids

73 FeNO: fractional exhaled nitric oxide

74 INTRODUCTION

75 Asthma represents one of the most common worldwide chronic diseases, affecting about 315
76 million of people (1). Epidemiological studies show that the severe form of this disease occurs in
77 about 3-10% of asthmatic patients (2). According to ATS/ERS guidelines (3) severe asthma is
78 characterised by poor control despite the maximal treatment, including high dose of inhaled
79 glucocorticoids (ICS) plus a second controller (usually a long-acting β_2 -agonist), and/or a long-
80 acting antimuscarinic agent, leukotriene receptor antagonist or theophylline. The definition of
81 severe asthma also includes the need for oral corticosteroids (OCS) therapy, as a regular treatment,
82 or taken at least twice in one year (3). Similarly, GINA recommendations include a treatment-based
83 severe asthma definition (4). Moreover, regardless of the chosen severe asthma definition, a crucial
84 role in the management of asthmatic patients, is played by the research and control of
85 comorbidities. The most frequent comorbidities are chronic rhinosinusitis with or without nasal
86 polyposis (5, 6), gastroesophageal reflux disease (7) and bronchiectasis (8). In addition, other
87 conditions have been highlighted as possible comorbidities of asthma, such as obesity, sleep apnea,
88 endocrine diseases and vocal cord disorders (9). Some authors have also investigated the possible
89 role of vitamin D both in childhood and in adulthood (10,11).

90 Despite its relatively low frequency, severe asthma has a substantial social impact, due to
91 chronic therapy, exacerbations (commonly requiring extra visits or emergency department
92 admissions), impairment in quality of life and OCS-related side effects (12), and is therefore

responsible for a not negligible socio-economic burden. Severe asthma accounts for about 50% of the overall direct and indirect costs of the disease (13).

In the last decade, several biological treatments were introduced and investigated in the field of severe asthma, with the aim of reducing exacerbations and OCS use. A more and more detailed knowledge of asthma pathophysiology paved the way to the development of targeted molecules, in particular within the frame of Th2 inflammation, which includes interleukin (IL) 4, IL-5, IL-9, IL-13 and airway epithelial cells or innate lymphoid cells-2 (14–17). In such case, the inflammatory background is responsive to ICS (18), which promote eosinophil apoptosis (19). Eosinophils exert a pivotal role in bronchial inflammation and represent one of the main targets for biological drugs. Mepolizumab (MEP), a IgG1/k class humanized monoclonal antibody, blocks circulating IL-5, which is responsible for eosinophils development, maturation and survival, was marketed in the last two years (20), thus, a large experience in real-life is now available. In Italy, the regulatory Agency requires a minimum threshold of 150 eosinophils/ μ L before prescription and 300/ μ L in the previous year, in addition to the clinical criteria of severe asthma (21). Despite the efficacy of MEP has been largely demonstrated in clinical trials only few data are available in the real-life setting (2,22–25). This retrospective observational study would add further data on the use of MEP in real-life.

METHODS

We describe herein the retrospective data analysis concerning severe asthmatic patients referring to eleven severe asthma centres in Italy (Genoa, Pietra Ligure, Milan, Cuneo, Turin, Reggio Emilia, Verona, Rome, Arenzano, Brescia) and treated with MEP for at least 12 months

(starting from 01st May 2017 to 31st December 2018). All centres shared a common database, which included the clinical and biological characteristics of the enrolled subjects. All patients fulfilled the criteria for severe uncontrolled asthma according to ATS/ERS guidelines (3) as well as MEP prescription rules according to Italian Drug Agency. In particular, patients had to have a peripheral blood eosinophil count above 300/ μ L in at least one occasion during the last year, and more than 150/ μ L before the first MEP injection. All patients were on the maximum inhaled treatment as per guidelines and on the minimum dose of OCS achievable to maintain the control. The adherence to treatment, correct use of devices, and doses were strictly assessed at the clinical visits. Also, whenever diagnosed or identified, comorbidities (smoking, gastroesophageal reflux, obesity, nasal polyposis, were addressed and treated before judging asthma as “severe” and before prescribing the biological agent. All the included patients received MEP 100 mg subcutaneously every 4 weeks for at least 12 months. At baseline and after 12 months of treatment all patients underwent spirometry according to ATS/ERS (26), and Global Lung Initiative reference values (27). The patient-reported perception of asthma control was assessed by the Asthma Control Test (ACT) (28). The possible presence of nasal polyposis was assessed by nasal endoscopy and/or paranasal sinuses computerized tomography in all patients. All patients signed an informed consent. Statistical analysis was performed by Fisher’s exact test, Chi-squared test, two-sided independent t-test or Mann-Whitney-U-test when appropriate. A $p < 0,05$ was considered as statistically significant.

RESULTS.

At December 31st 2018, 138 severe asthmatic patients (78 female; mean age 58 ± 10 years; age range 21-81), treated for at least 12 month with MEP, were included. The average onset of the

134 disease was 34 ± 16 years (range 4-61) with a mean duration of 30 ± 21 years. Former smokers
135 accounted for 16% of the whole sample. Mean baseline blood eosinophils level was $822 \pm 491/\mu\text{L}$ at
136 baseline, and decreased to $117 \pm 96/\mu\text{L}$ after 1 year of MEP treatment ($p < .0001$) (**Figure 1A**).
137 Twenty seven patients (19.5%) were allergic. Rhinitis, nasal polyposis (59%) and gastroesophageal
138 reflux disease were the most common comorbidities, as already reported in literature (29) . Some
139 patients also suffered from atopic dermatitis (7%), and bronchiectasis were detected in 18% of
140 patients. 5 patients (4%) and 31 (22%) were receiving oral theophylline and leukotriene antagonists,
141 respectively. Of note, 18/138 patients had previously received Omalizumab, with no benefit. The
142 main clinical characteristics of patients are summarized in **Table 1**.

143 The exacerbation rate at baseline was $3.8 \pm 2.5/\text{year}$, and decreased by 81% with a mean of
144 $0.7 \pm 1.1/\text{year}$ ($p < .0001$) at the 12 months follow-up. Also the hospitalization rate decreased from 0.4
145 ± 0.7 episodes per year at baseline, to 0 at the 12-year follow-up ($p < .0001$) (**Figure 1B-C**)
146 Before MEP 80% patients were on regular systemic steroid therapy, with a mean daily dose of 10.1
147 mg prednisone or equivalent (range 0 – 40). After 12 months only 28% of patients still remained on
148 daily OCS, with a significant mean dose reduction to 2.0 mg/day ($p < .0001$).

149 Lung function tests showed an average increase of 340 mL in FEV1 at the 12 months
150 follow-up, reaching a statistically significant difference compared with the baseline ($p = .0001$)
151 (**Figure 1D**). Statistic significant change not achieved for the forced vital capacity (baseline
152 $3.16 \pm 1.05 \text{ L}$ VS follow up $3.32 \pm 1.06 \text{ L}$; $p = 0.231$). The ACT mean score significantly increased
153 from 17 ± 5 to 22 ± 3 ($p < .0001$) (**Table 1**). We attempted a sub analysis, comparing patients with
154 eosinophils $< 500/\mu\text{L}$ or $\geq 500/\mu\text{L}$. There was no statistical difference between the two groups at

155 baseline and at post treatment ($p > 0.05$) in: exacerbations, dose of OCS, ACT, days of hospital stay,
156 whereas all the statistical significances were maintained in the two group at pre VS post treatment
157 **(Repository table 1).**

158 The occurrence of adverse events was low, the most common being local site injection
159 reactions (4.3%). Only in one case hospitalization was required because of a paroxysmal
160 supraventricular tachycardia onset few days after the second MEP administration. This episode was
161 judged as not related to treatment, and the drug administration was continued. The observed adverse
162 events during treatment are summarized in **Table 2.**

163 **DISCUSSION**

164 Several clinical trials clearly proved the safety and efficacy of MEP. However, it is well
165 known that real-life setting data may significantly differ from those of the clinical trials, in term of
166 patients characteristics or follow-up and outcome modality (30). Therefore, real-life evidence
167 should be provided to support the results of regulatory trials, and to add new knowledge. It is
168 noteworthy that the patients observed in real life, differ in clinical characteristics from those
169 described in the regulatory trials that lead to the commercialization of the therapy (23). The efficacy
170 of MEP in reducing exacerbations was first evaluated by using intravenous (IV) formulation in the
171 DREAM (15) study, which showed a reduction of 48% vs placebo in active arm. A further study,
172 MENSA (16) compared intravenous and subcutaneous administration with placebo, and an
173 exacerbation reduction rate of 53% with the 100 mg subcutaneous route was demonstrated. In this
174 retrospective observational study, the efficacy of subcutaneous administration of MEP 100 mg/4
175 weeks in severe uncontrolled asthmatic patients with high blood eosinophil levels was confirmed,

and led to the introduction in commerce and definition of prescription plans. The exacerbation rate, that is the most relevant clinical parameter for its socio-economic burden, was significantly decreased in the treated subjects. In fact a 81% reduction of the exacerbations after one year of MEP could be ascertained, together with a substantial reduction of hospitalizations rate (89%). When comparing the exacerbation rate in the published clinical trials and the present survey, a larger impact of the biologic treatment was detected. As above mentioned, the MENSA study reported 53% reduction compared with the placebo group (16) whereas in our real-life setting study the reduction was 81%. Another interesting observation concerns the effect of MEP on OCS daily intake. This effect was described by Bel et al in the SIRIUS trial (17), with a reduction by 50% of the dose of OCS, and we could document a 80% decrease in the daily dose intake after 12 months of therapy in the real-life setting. Also this aspect is of relevance under the economic viewpoint (31). According to experimental data, both the reduction of exacerbations and the mean OCS dose are greater in patients in real life and a greater magnitude of efficacy of MEP could depend on the baseline eosinophilic inflammatory status, although the data shown in the repository **table 1** do not demonstrate a correlation between the clinical response and the level of blood eosinophils.

Regarding asthma symptoms, MEP produced a significant ACT score improvement (16 to 23; $p < .0001$). Furthermore the Delta ACT in real life resulted higher than the accepted minimal clinically important difference of 3 points (32). As previously described there was an increase in FEV₁, that did not reach a statistical significance ($p = .092$). Nevertheless, from a clinical viewpoint an increase of 340 ml in FEV₁, is not negligible, since it overcomes the normal variability (33). The effect of MEP on nasal polyposis history in the enrolled patients is not so clear-cut, but this was not an

objective of the study. Some improvement in nasal symptoms was self-reported by some patients, although an imaging or endoscopy pre VS post was not done. On the opposite, the impact of MEP on atopic dermatitis was clinically more apparent, despite in our population, the affected patients were only 9 (7%). Finally, it is noteworthy that the 27 patients who previously failed to respond to Omalizumab, had all a significant benefit with MEP, as already described (34).

The occurrence of adverse events was low. The most frequently reported side effects in clinical trials were headache, naso-pharyngitis, urticaria, arthralgia (35-36). In our population, the most frequent side effects (4.3%), were negligible local reactions at the injection site, myalgia and arthralgia.

It is now accepted that studies in real-life have an emerging scientific dignity, since they can provide useful clinical information, not available in the controlled trials (37). In fact, in the real-life setting, patients often differ in their characteristics from those selected with the rigid criteria employed in trials for registration (30). Especially for the expensive biological agents proposed for severe asthma, real-life observations could help in refining the prescription criteria and improving the use of resources. A composite index including different biomarkers may represent a potential tool in order to better predict the response to these drugs as suggested , for instance, in COPD (38) and in Idiopathic Pulmonary Fibrosis (39).

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Characteristics	Baseline (n= 138)	12 months (n=138)	Difference	p-value
Blood eosinophils mean(range)	822 (150-3060)	117 (0-600)	-705 (86%)	<.0001
Median (SEM)	800 (41.78)	100 (8.19)		
Exacerbations/12y mean (SD)	3.8 (2.5)	0.7 (1.1)	-3.1 (81%)	<.0001
Median (IQ RANGE)	3.0 (2.8)	0 (1.0)		
Hospitalizations 12y (mean ± SD)	0.4 (0.7)	0.0 (0.2)	-0.4 (89%)	<.0001
OCS dependent n (%)	111 (80)	38 (28)	-73 (66%)	<.0001
OCS mg/day, mean (SD)	10.1 (9.4)	2.0 (4.2)	-8.1 (80%)	<.0001
LAMA (%)	51 (37)	51 (37)	-	-
Rhinitis (%)	90 (65)	82 (59)	-8 (9%)	.385
Nasal Polyposis (%)	81 (59)	80 (58)	-1 (1%)	.999
GERD (%)	43 (31)	33 (24)	-10 (23%)	.225
Atopic dermatitis (%)	9 (7)	4 (3)	-5 (55%)	.255
Bronchiectasis (%)	25 (18)	25 (18)	-	-
FEV1 (L±SD)	2.03 (0.78)	2.36 (0.88)	0.34 (17%)	.001
FEV1 (%)	69	75	5.6 (8%)	< .0001
FVC (L±SD)	3.16 (1.05)	3.32 (1.04)	0.16 (5%)	.231
FVC (%)	88	92	4.4 (5%)	.021
FEV1/FVC (±SD)	0.65 (0.11)	0.69 (0.11)	0.04 (6%)	.002
FeNO (SD)	75 (53)	42 (36)	-33 (44%)	<.0001
Median (SEM)	64 (4)	30 (3)		
ACT (±SD)	17 (5)	22 (3)	5 (34%)	<.0001

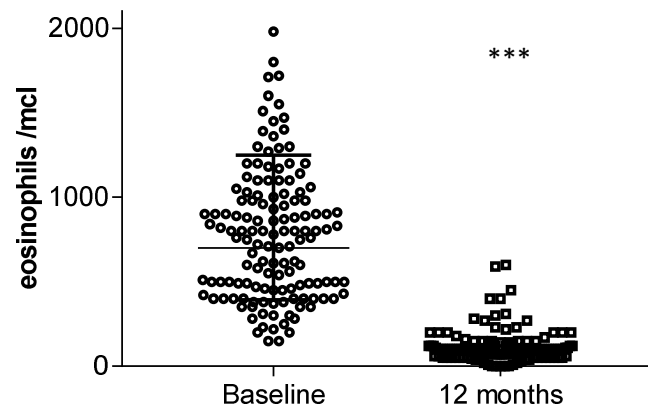
319 **TABLE 1:** main characteristics of the patients at baseline and after 12 months of therapy.

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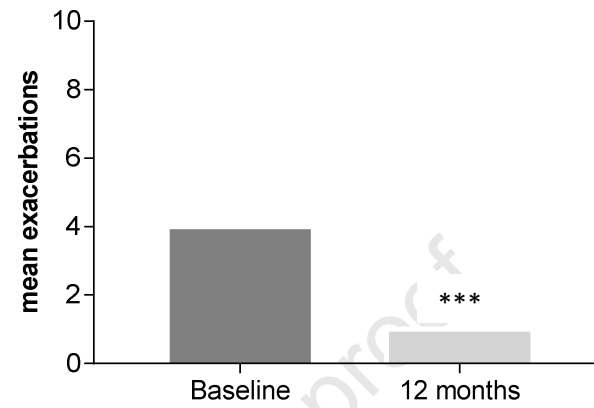
Table 2. Summary of observed adverse events

Event	no. of patients (%)
Paroxysmal supraventricular tachycardia (PSVT)	1 (0.7)
Local site injection reaction	6 (4.3)
Diarrhoea	1 (0.7)
Myalgia/ arthralgia	2 (0.7)
Headache	1 (0.7)
Dizziness	1 (0.7)
Urticaria	1 (0.7)
Cystitis	1 (0.7)

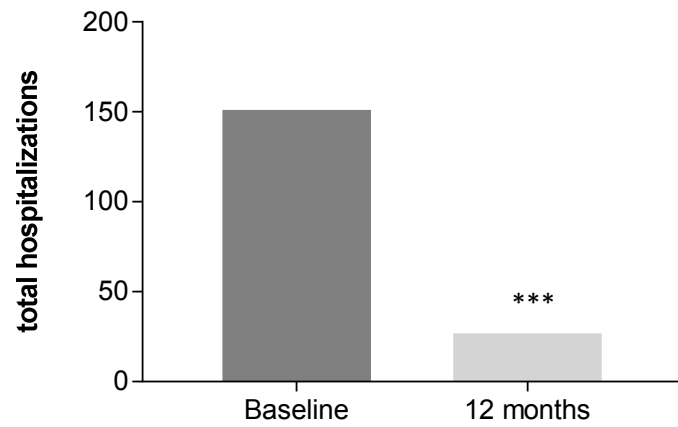
TABLE 2: Summary of observed adverse events



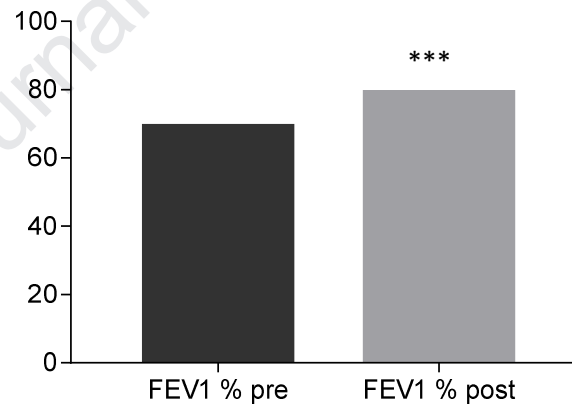
(A)



(B)



(C)



(D)

Figure 1. (A) Decreasing of eosinophils blood count after 12 months of therapy. (B) Mean of exacerbations at baseline and after 12 months of therapy. (C) Total number of hospitalization before and after mepolizumab therapy. (D) Variation of lung function expressed in FEV₁. *** indicates a $p < .0001$.

Repository Table 1.

Patients differentiation according to eosinophils level, before and after 12 months of MEP administration.

	PRE MEP			POST MEP		
	< 500 eos/ μ L (n= 41)	> 500 eos/ μ L (n= 97)	> 400 eos/ μ L (n= 109)	< 500 eos/ μ L	> 500 eos/ μ L	> 400 eos/ μ L
Age (range)	57 (7-45)	58 (21-81)	58 (21-81)	-	-	-
Age onset	40 (15.0)	32 (16.6)	32 (16.7)	-	-	-
Exacerbations/12y mean Median (IQ RANGE)	3.61 (2.55) 3 (2)	3.89 (2.52) 3 (3)	3.83 (2.49) 3 (3)	0.78 (1.09) 0 (1)	0.72 (1.16) 0 (1)	0.73 (1.15) 0 (1)
Number of hospitalization	0.46 (0.7)	0.37 (0.66)	0.35 (0.64)	0.07 (0.34)	0.03 (0.17)	0.03 (0.16)
OCS (mg prednison)	10.46 (10.17)	9.97 (9.1)	9.66 (8.92)	2.62 (4.9)	1.79 (3.9)	1.75 (3.8)
FEV1 (L)	2.01 (0.57)	2.04 (0.86)	2.01 (0.82)	2.32 (0.71)	2.38 (0.94)	2.35 (0.92)
FEV1 (%)	71 (19)	69 (20)	68 (20)	80 (18)	79 (18)	79 (18)
FVC (L)	3.17 (0.84)	3.16 (1.13)	3.13 (1.09)	3.29 (0.89)	3.34 (1.12)	3.31 (1.11)
FVC (%)	89 (17)	88 (19)	87 (18)	93 (15)	93 (18)	93 (18)
FEV1/FVC	0.64 (0.12)	0.65 (0.11)	0.65 (0.11)	0.70 (0.14)	0.68 (0.10)	0.68 (0.11)
FeNo Median (SEM)	65 (47) 49 (7)	79 (54) 73 (5)	77 (53) 70 (5)	43 (34) 32 (5)	42 (38) 38 (4)	42 (38) 30 (4)
Blood eosinophils mean (range) Median (SEM)	365 (150-490) 400 (15)	1015 (500-3060) 900 (47)	955 (420-360) 880 (45)	119 (0-600) 100 (17)	116 (0-590) 100 (9)	122 (0-600) 100 (10)
ACT	17 (5.3)	17 (4.7)	17 (4.7)	22 (2.8)	22 (2.6)	23 (2.6)

All data has been reported as mean and standard deviation, where not otherwise specified.