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This is the peer reviewed (post-print) version of the following article:

Original
Mepolizumab for severe eosinophilic asthma: a real-world snapshot on clinical markers and timing of response / Caminati, M., Cegolon, L., Vianello, A., Chieco Bianchi, F., Festi, G., Marchi, M.R., Micheletto, C., Mazza, F., Tognella, S., Senna, G.. - In: EXPERT REVIEW OF RESPIRATORY MEDICINE. - ISSN 1747-6348. - STAMPA. - 13:12(2019), pp. 1205-1212. [10.1080/17476348.2019.1676734]

Availability:
This version is available at: 11368/2999482 since: 2021-11-29T21:09:06Z
Publisher:

Published
DOI:10.1080/17476348.2019.1676734
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28 November 2026

arTs Università degli Studi di Trieste
Archivio della ricerca – postprint

Mepolizumab for severe eosinophilic asthma: a real-world snapshot on clinical markers and timing of response

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ABSTRACT

Background: Few studies have provided real-world evidence of mepolizumab efficacy and safety. We aimed to evaluate mepolizumab for severe eosinophilic asthma in daily clinical practice.

Research design and methods: Patients included in the RINOVA (Interdisciplinary Network for the management of severe asthma in Veneto region, Italy) database were investigated. Blood eosinophil count, forced expiratory volume in 1 second, % of predicted (FEV1%), fractional exhaled nitric oxide (FeNO), asthma control test (ACT), oral steroid (OCS) intake, and exacerbation rate were evaluated during mepolizumab treatment.

Results: 69 patients were enrolled (mean age: 55.1 years; 60.9% females). A significant improvement was detected at one month with respect to blood eosinophils (median level at baseline: 710/μl; −620/μl, $p < 0,001$), FEV1% (median value at baseline 87; range: 79–101; +4, $p = 0.001$) and ACT (median value at baseline 18; range: 14–20.5;+4, <0.001). A significant reduction of FeNO was observed six months after the treatment start, when the exacerbation rate and the mean OCS dose significantly decreased (respectively: Δ reduction −3; $p < 0.001$ and −5 mg; $p < 0.001$).

Conclusions: Our study provides real-world evidence of mepolizumab safety and confirms its dramatic steroid sparing effect. The greatest clinical change (ACT and FEV1) was observed within the first month.

ARTICLE HISTORY
Received 21 April 2019
Accepted 2 October 2019

KEYWORDS
Severe asthma; eosinophils; mepolizumab; asthma network; real-world evidence

1. Introduction

Asthma is a common respiratory disease and its worldwide prevalence ranges from 5% to 8% in the general population [1]. Most of the patients can be controlled by the inhaled treatment, but 5–10% of them suffer from severe asthma [2]. The patients affected by severe asthma need for high doses of inhaled corticosteroids (ICS), long-acting beta agonists (LABAs) plus one or two controllers such as montelukast and/or tiotropium. Despite this regular therapy, some patients remain uncontrolled and experience frequent exacerbations, requiring admissions to the emergency departments and regular or intermittent bursts of oral corticosteroids (OCS). The identification of the specific disease phenotype is critical in these patients, especially in order to identify potential candidates to the new biologic drugs as an add-on therapy [2]. Omalizumab, which was the first biologic drug available on the market for the treatment of severe allergic asthma, is an anti-IgE humanized monoclonal antibody [3]. More recently mepolizumab, a humanized anti-interleukin 5 (IL5) IgG1/k antibody, was introduced for the severe eosinophilic asthma phenotype. In fact, IL5 plays a key role in that condition as a modulator of eosinophils development at any step, including maturation in the bone marrow, activation, chemotaxis, survival, and proliferation [4]. Several controlled studies have proved the efficacy and safety of mepolizumab in severe eosinophilic asthma [5–12]. The reduction of the exacerbation rate [5–8; 10–12] and the decrease of OCS use [6,9] were reported as the main positive outcomes. A less impressive effect on lung function was also observed [8]. In all the studies, a substantial fall in blood eosinophils was described [5–8]. However, more positive results were observed in patients with eosinophilic count ≥300 cells/μl, which is the current cutoff required by the Italian National Health Service (NHS) for the mepolizumab use in clinical practice [7–9]. However, the recent literature has pointed out that the different setting which characterizes the controlled trials and the real-life studies is relevant and may impact on the final treatment-related outcomes. Thus, the results of controlled studies need to be confirmed in the real-life setting [13,14]. Under this perspective, our real-life multicenter study aimed to evaluate the clinical efficacy and the safety of mepolizumab, as well as the timing of the treatment outcomes, in a group of patients with severe refractory eosinophilic asthma during a 6 months treatment frame.

Article highlights

- Several controlled studies have proved the efficacy and safety of mepolizumab in severe eosinophilic asthma. The reduction of the exacerbation rate, the decrease of OCS use, and to a less extent the lung function improvement represented the main clinical outcomes.
- The different setting which characterizes the controlled trials and the real-life studies may impact on the final treatment-related outcomes. Thus, the results of controlled studies need to be confirmed in the real-life setting. Up to now, the real-world evidence about mepolizumab is small.
- Our study, to the best of our knowledge including up to now the largest population in real life, confirmed mepolizumab efficacy and rapid clinical effect, without any adverse events.
- The greatest clinical change in terms of FEV1 and ACT in comparison with the baseline values was observed within the first month after the treatment start
- Over a 6 months follow-up, a dramatic steroid-sparing effect and exacerbation rate decrease were observed.

The definition of responder or nonresponder to the treatment, and therefore the decision about treatment continuation, should include a global evaluation and should be tailored according to each patient's profile.

2. Patients and methods

A retrospective analysis of the RINOVA database was carried out. RINOVA (Interdisciplinary Network for the management of severe asthma in Veneto region, Italy), an implementation of NEONet – North East Omalizumab Network [15], is a nonprofit network project including 6 Allergy and Respiratory Referral Centers for Severe Asthma located in the Northeast region of Italy and approved by the local ethics committee. RINOVA aims to collect real-life but standardized clinical information from adult patients affected by severe asthma and treated with mepolizumab, in order to provide real-world evidence. RINOVA project intends to address the current unmet needs regarding biologics in severe asthma, including specific clinical outcomes and timing of response, the impact on comorbidities, the long-term follow-up of treated patients, the predictors of response, and the optimal treatment duration. The participating clinicians, once obtained informed consent from the patients, enter anonymous coded data into a shared limited-access web platform. The inclusion criteria were the following: (1) A confirmed diagnosis of severe asthma according to the ERS/ATS definition [2]; (2) Eligibility to mepolizumab treatment, according to the prescription requirements established by the European Regulatory Agency [16] (>150 eosinophils/μL when recruited and at least 300 cells/μL within the twelve months prior to treatment start).

Each patient received as add-on therapy mepolizumab 100 mg, which was administered subcutaneously every four weeks.

Lung function assessment, FeNO measurement, and asthma control test were evaluated at baseline, and 1, 3, and 6 months after the treatment start. Eosinophils blood count was performed at baseline, and 1 and 6 months after the treatment start. Oral steroid intake and exacerbation rate in the previous 12 months were recorded at baseline, and 6 months after the treatment start.

The study was carried out according to the principles of the Declaration of Helsinki and received the approval of the local Ethic Committee. A written informed consent was obtained from each participant to the study.

2.1. Statistical analysis

Blood eosinophilia (cells/μl), asthma control test (ACT), oral steroid (OCS) dose (mg), predicted value of the forced expiratory volume during the first second (FEV1%) and exhaled nitric oxide (FeNO) in parts per billion (ppb) were measured at baseline and after different intervals (1, 3, 6 months), depending on the clinical parameter. The respective mean and median for all continuous parameters were calculated. Since none of the available parameters was normally distributed, the Wilcoxon nonparametric test was employed to contrast differences at various intervals. Differences in proportions were also assessed for categorical data. All comparisons were made with the respective baseline values. The level of significance of all tests was set at 0.05.

3. Results

Overall 69 patients were enrolled and investigated, 33 by Allergy Units and 36 by Respiratory Medicine Units. Demographic data are shown in Table 1. A prevalence of females was observed (60.9%). The mean age was 55.1 (range 21.1–80.5 years) and body mass index (BMI) was 24 ± 3.8 (range 17.3; 35.4). Nasal polyps were detected by nasal endoscopy in 42 patients (60.9%); among them 5 patients (12.0%, 7.2% of the whole study population) suffered from aspirin intolerance. All the patients were on regular treatment with a combination of ICS (mean dose: 1085.4 ± 481.2 mcg of fluticasone propionate equivalents) plus long-acting β-agonists (LABA). Furthermore, in 40.3% of patients the pharmacological treatment also included a leukotriene receptor antagonist and in 37.9% a long-acting muscarinic antagonist. The whole sub-population with nasal polyps had been prescribed topical nasal steroids. All the patients were using OCS, on regular basis or intermittently. Table 1 reports the distribution of the considered clinical variables at baseline and following time-points, expressed as mean and median.

Table 2 summarizes how the different parameters have changed during the treatment course, within the study timeframe. The median blood eosinophils level at baseline was 710/μl, showing a substantial depletion at the first month assessment (−620/μl, $p < 0.001$) with no significant further changes at the six months recording (mean value 130/μl). The baseline FEV1% median value (87; range: 79–101) significantly increased at the first time-point assessment (1 month: +4, $p = 0.001$), it showed a plateau during the remaining study time frame but maintained a significant improvement in comparison with baseline (3 months: +3, $p = 0.001$; 6 months: +5, $p = 0.001$) (see also Figure 1). The proportion of subjects with FEV1% <80 significantly decreased from 63.1% at baseline to 50.0% at month 1 ($p < 0.001$), 54.0% at month 3 ($p < 0.001$) and to 57.1% at month 6 ($p < 0.001$). However, a clinically significant increase (> 15%) was registered in 38.7% of patients after six months.

The median FeNO value before the treatment start was 73.0 ppb and a statistically significant reduction was observed only six months after treatment started (−18 ppb, $p > 0.001$) (see also Figure 2). The proportion of subjects with FeNO >40 ppm was 79.7% at baseline, significantly increasing to 85.4% after

Table 1. Distribution of factors; Number (N), percentage (%); mean ± SD; median (interquartile (IQ) range); M = missing values.

VARIABLES		Baseline	Month 1	Month 3	Month 6
Sex	Female – N (%)	42 (60.9%)			
	Male – N (%)	27 (39.1%)			
Age (years)	Mean ± SD	55.4 ± 11.9			
	Median (IQ)	54.5 (49.3; 64.7)			
Poliposis	No – N (%)	27 (36.1%)			
	Yes – N (%)	42 (60.9%)			
BMI *(m/Kg^2)	Mean ± SD	24 ± 3.8			
	Median (IQ)	23.7 (17.3; 35.4)			
Eosinophils (blood count/μL)	Mean ± SD	983 ± 1021.3	181.6 ± 172.1		130.5 ± 192.3
	Median (IQ)	710 (405; 1,010)	145 (90–200)		90 (60–150)
	Missing values	5	19		10
FEV1% *	Mean ± SD	73.1 ± 18.9	78.1 ± 16.3	78.7 ± 18.2	79.4 ± 19.1
	Median (IQ)	76 (59; 88)	79 (65.5; 87.5)	79 (65; 94)	77 (65; 98)
	<80 – N (%)	41/65 (63.1%)	28/56 (50.0%)	34/6 (54.0%)	36/63 (57.1%)
	Missing values	4	13	6	6
Tiffeneau index	Mean ± SD	64.7 ± 10.2	67.9 ± 8.9	67.0 ± 12.6	67.4 ± 10.8
	Median (IQ)	64.9 (58.9; 71.4)	66.8 (63.5; 74.0)	68.7 (62.3; 74.7)	67.9 (61.7; 75.2)
	Missing values	5	14	6	6
Asthma Control Test (ACT)	Mean ± SD	16.8 ± 4.8	21.4 ± 3.2		22.9 ± 3.3
	Median (IQ)	18 (14; 20.5)	22 (20; 24)		24 (22; 25)
	<20 – N (%)	43/64 (67.2%)	9/52 (17.3%)		5/52 (9.6%)
	Missing values	5	17		17
Exhaled Nitric Oxide (FeNO) (ppb)	Mean ± SD	77.7 ± 44.5	85.4 ± 58.4	72.9 ± 49.6	60.2 ± 45.7
	Median (IQ)	73 (45.8; 98)	73 (47.3; 95.5)	62 (36.5; 98.5)	50 (28.5; 73)
	≥ 40 – N (%)	47/59 (79.7%)	41/48 (85.4 %)	41/58 (70.7%)	35/57 (61.4%)
	Missing values	10	21	11	12
Oral Cortiso-steroid Therapy (OCS)	Yes – N (%)	43/61 (70.5%)			19/59 (32.2%)
	Mean ± SD	8.5 ± 8.8 mg			1.4 ± 2.2
	Median (IQ)	5 (0; 12.5) mg			0 (0; 2.5)
	Missing values	8			10
Relapses (number)	Yes – N (%)	64/68 (94.1%)			26/65 (40.0%)
	Mean ± SD	4.9 ± 3.4			0.6 ± 1.4
	Median (IQ)	4 (3; 6)			0 (0; 1)
	Missing values	1			4

* BMI = body mass index
** FEV1% = forced expiratory volume during the first second (percentage of the predicted value

Table 2. Variation of different clinical parameters from baseline to month 1, 3, and 6.

VARIABLES		Baseline values	CHANGE AT MONTH 1		CHANGE AT MONTH 3		CHANGE AT MONTH 6	
			Estimates	p-value	Estimates	p-value	Estimates	p-value
Eosinophils (blood count/μL)	Median (IQ)	710 (405; 1,010)	−620 (−950; −360)	<0.001*			−620 (−910; −300)	<0.001*
FEV1%	Median (IQ)	76 (59; 88)	+4 (−2; 14)	0.001*	+3 (−1; 12)	0.001*	+5 (−4; 13.5)	0.001*
	<80 – N(%)	41/65 (63.1%)	28/56 (50.0%)	NS **	34/63 (54.0%)	NS **	36/63 (57.1%)	NS **
ACT	Median (IQ)	18 (14; 20.5)	+4 (1; 8)	<0.001*			+6 (2; 10)	<0.001*
	<20 – N(%)	43/64 (67.2%)	9/52 (17.3%)	<0.001**			5/52 (9.6%)	<0.001**
FeNO (ppb)	Median (IQ)	73 (45.8; 98)	−4 (−23; 7)	NS	−11.5 (−28; 9)	0.045*	−18 (−38; −2)	0.001*
	> 40 N(%)	47/59 (79.7%)	41/48 (85.4%)	NS**	41/58 (79.7%)	NS**	35/57 (61.4%)	0.015**
Relapses (Number)	Median (IQ)	4 (3; 6)					−3 (−5; −2)	<0.001*
	Patients – N(%)	64/68 (94.1%)					26/65 (40.0%)	<0.001**

* Wilcoxon test p-value (difference from baseline)
** difference in proportions
Number, percentage of patients (%); median; interquartile range (IQ); Wilcoxon test p-value. NS = nonsignificant. ACT = asthma control test; FEV1% = exhaled expiratory volume during the first second (percentage of predicted value); FeNO = exhaled nitric oxide.

one month, decreasing to 79.7% after three months and further reducing to 61.4% after six months.

ACT median score showed the greatest change 1 month after the treatment start (+4; <0.001), with a less evident improvement at 6 months (+6; $p < 0.001$), though still significant in comparison with baseline (see also Figure 3). The baseline proportion of patients showing ACT <20 was 67.2%, reducing to 17.3% at month 1 ($p < 0.001$) and to 9.6% at month 6 ($p < 0.001$).

The median number of relapses before mepolizumab treatment was 4/year. After 6 months from the treatment start a significant decrease was registered (Δ reduction −3; $p < 0.001$). The proportion of subjects with asthma relapses at baseline was 94.1% and decreased to 40.0% after 6 months ($p < 0.001$).

Table 3 reports the variation of OCS treatment during mepolizumab treatment course. At baseline, the median dosage of OCS was 5 mg of prednisone or equivalents. After 6 months the initial dosage significantly decreased (−5 mg; $p < 0.001$). The proportion of patients on daily OCS therapy was 70.5% at baseline, reducing to just 32.2% after 6 months. Only 2 patients were still on daily OS therapy at 6 months evaluation

In order to evaluate the potential impact of nasal polyps on the treatment effect, a direct comparison between patients with and without polyposis including the main clinical

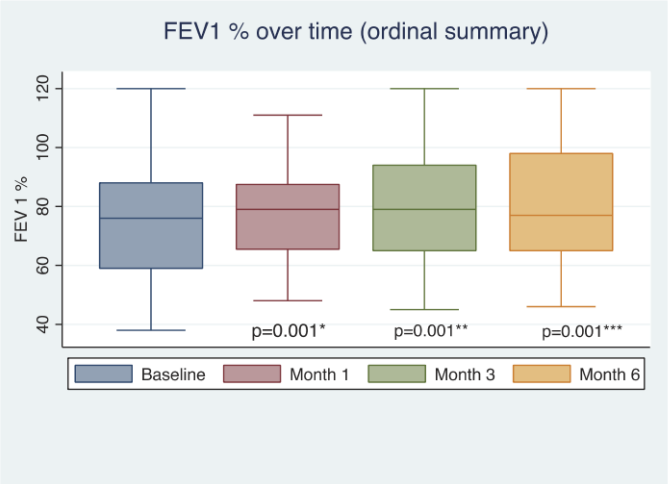


Figure 1. Box plot displaying the nonparametric summary of the percentage of predicted value of Forced Expiratory Volume during the first second (FEV1%) at baseline and after 1, 3 and 6 months of treatment with Mepolizumab. Median, interquartile range and lower/upper limits.

Wilcoxon test p-value for the difference in FEV1 between:* baseline and month 1** baseline and month 3*** baseline and month 6

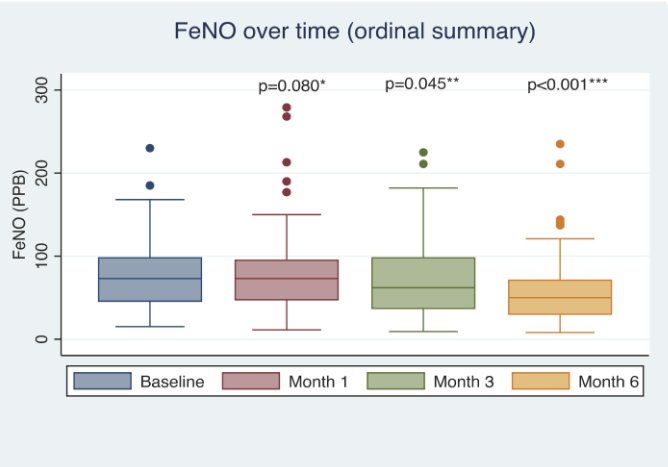


Figure 2. Box plot displaying the nonparametric summary of the fractional exhaled nitric oxide (FeNO) at baseline and after 1, 3, and 6 months of treatment with mepolizumab. Median, interquartile range, and lower/upper limits. PPB = Parts per Billion.

Wilcoxon test p-value for the difference in FEV1 between:* baseline and month 1** baseline and month 3*** baseline and month 6

outcomes was performed. Table 4 shows similar improvement in the two subpopulations in terms of blood eosinophils count and ACT score. Patients without polyps were characterized by a lower baseline FEV1% and a more significant improvement of the same parameter could be observed after 6 months in comparison to the patients with nasal polyps.

A global evaluation of clinical response to mepolizumab was also performed. In particular, the proportion of nonresponder patients, partially responder and fully responders was evaluated by considering the presence of relapses (yes/no), FEV1% < or ≥80 and ACT score < or ≥20. As Table 5 shows, the majority of patients (53.3%) fully responded to mepolizumab treatment after 6 months (no relapses recorded, FEV1 ≥ 80 and ACT ≥20), whereas nonresponders (relapses, FEV1 < 80 and ACT <20) were

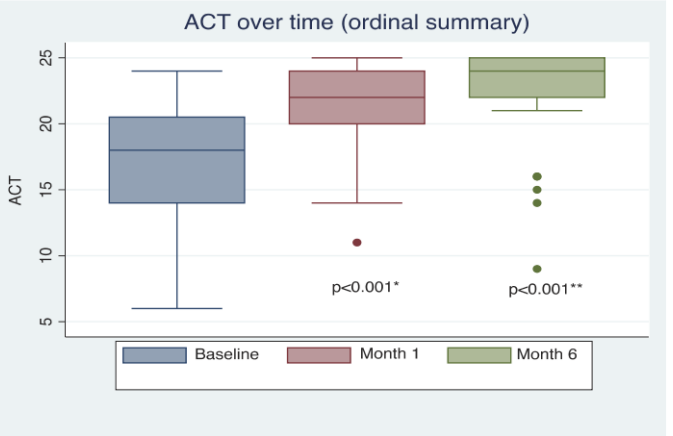


Figure 3. Box plot displaying the non parametric summary of asthma control test (ACT) at baseline and after 1 and 6 months since treatment start with mepolizumab. Median, interquartile range and lower/upper limits.

Wilcoxon test p-value for the difference in FEV1 between:* baseline and month 1** baseline and month 6

Table 3. Patients on oral corticosteroid (OCS) therapy, from baseline to month 6.

Categories of patients on OCS therapy	Baseline	Change at Month 6	p-value
Patients on OCS therapy	43/61 (70.5%)	19/59 (32.2%)	<0.001*
OCS dosage (mg) – Median (IQ)	5 (0; 12.5)	−5 (−10; 0)	< 0.001**
Patients maintaining the initial OCS regimen		2/42 (4.8%)	
Patients reducing the initial OCS dose by 50–74%		6/42 (14.3%)	
Patients reducing the initial OCS dose by 75–99%		10/42 (23.8%)	
Patients fully suspending the initial OCS regimen		24/42 (57.1%)	

* Difference in proportions
** Wilcoxon test p-value
Number, percentage (%); median with interquartile range (IQ).

only 6.0%. The rate of partial responders at 6 months was 54.0%. Table 5 also reports the rate of response to mepolizumab after 1 month. 8.5% patients were non responders at month 1, having both FEV1%<80 and ACT score <20. However, 75% of the latter subgroup still showed some improvement at 6 months, becoming partial responders. At month 1, the rate of partial responders (46.8%) was slightly higher than full responders (44.6%). The vast majority of patients of both categories tend to maintain their response after 6 months, especially fully responders (81.8%), suggesting early efficacy of mepolizumab in asthma control.

No local or systemic adverse events were recorded during the treatment course.

4. Discussion

Our observational study investigated the efficacy of mepolizumab as a treatment for severe eosinophilic asthma in a real-life setting. It focused in particular on specific clinical outcomes and their timing of change from the treatment start, within a 6-months observation period. The greatest improvement in terms of lung function, ACT score, and blood eosinophilia was detected since the first follow-up visit, on month after the treatment start. After that, a less evident change, but still significant in comparison with baseline, was observed. With regard to FeNO,

Table 4. Comparison of different clinical parameters from baseline to month 6, by nasal poliposis.

		PATIENTS WITHOUT POLYPS (N = 27)			PATIENTS WITH POLYPS (N = 42)		
FACTORS	ESTIMATES	BASELINE	MONTH 6	P value	BASELINE	MONTH 6	P value
FEV1%	Median (IQ)	64 (56; 81)	+5 (1;17)	0.006*	77 (65; 92)	+4 (−7; 11)	NS*
	Decrease/no change		6/25 (24.0.%)			13/35 (37.1%)	NS@
	increase by 1–14%		9/25 (36.0%)			12/35 (34.3%)	
	increase ≥ 15%		10/25 (40.0%)			10/35 (28.6%)	
ACT < 20	N of patients (%)	19/25 (76.0%)	3/22 (13.6%)	<0.001**	24/39 (61.5%)	2/30 (6.7%)	<0.001**
Blood Eosinophils	Median (IQ)	830 (410; 1,170)	−815 (−1,105; −420)	<0.001*	700 (400; 980)	−600 (−910; −350)	<0.001*

• Wilcoxon test p value;
@ Chi square test p value (association of nasal poliposis with FEV1% variation)
** Difference in proportions
Number (N), percentage (%), median, interquartile range (IQ). ACT = asthma control test; FEV1 = exhaled expiratory volume during the first second.

Table 5. Category of patients, by response to mepolizumab treatment, Number, percentage (%).

CATEGORY OF PATIENTS	MONTH 1	MONTH 6	
Non responders		Relapses, ACT <20, FEV1% <80	3/50 (6.0%)
Partial responders		Relapses, ACT<20, FEV1% ≥80	1/50 (2.0%)
		Relapses, ACT ≥20, FEV1% <80	12/50 (24.0%)
		Relapses, ACT ≥20, FEV1% ≥80	2/50 (4.0%)
		Relapse free, ACT ≥20, FEV1%<80	12/50 (24.0%)
Fully responders		Relapse free, ACT ≥20, FEV1% ≥80	20/50 (40.0%)
Nonresponders@	4/47 (8.5%)	Nonresponders@	1/4 (25.0%)
		Partially responders#	3/4 (75%)
		Fully responders*	0
Partial responders#	21/47 (46.8%)	Nonresponders@	2/21 (9.5%)
		Partially responders#	16/21 (76.2%)
		Fully responders*	3/21 (14.3%)
Fully responders*	22/47 (44.7%)	Nonresponders@	0
		Partially responders#	4/22 (18.2%)
		Fully responders*	18/22 (81.8%)

@ Patients both with FEV1% <80 and ACT<20.
# Patients with either FEV1% <80 or ACT <20.
* Patients with both FEV1% ≥80 and ACT ≥20.

a statistically significant reduction was observed only at the six months assessment. At the same time-point, the median number of exacerbations and the median dosage of OCS also significantly decreased. Of note only 2 subjects were still on daily OCS therapy at the 6 months evaluation.

The efficacy and safety of mepolizumab as a treatment option for severe eosinophilic asthma in patients with at least 300 eosinophils/μL in the blood has been proved by several trials [5–12]. In particular, the clinical impact of mepolizumab has been described in terms of steroid-sparing effect, health-related QoL improvement, pre-bronchodilator FEV1 increase, and annual exacerbation rate reduction.

However, it has been highlighted that randomized clinical trials are needed to prove efficacy and safety of new drugs, but cannot address some issues strictly connected with the real-life setting. The identification of responders, the optimal treatment duration, the impact of the treatment on comorbidities, its long-term safety and tolerability (including the definition of potential risk factors for adverse events), the long-term dropout analysis and the reasons for that are part of the un-answered questions the physicians face in their daily practice [13,14].

Furthermore the different study setting characterizing clinical trials and real-life studies may significantly impact on the clinical treatment outcomes, mainly due to substantial differences in the study populations in terms of age, comorbidities profiles, and treatment prescription criteria [13,14]. In fact, patients enrolled in clinical trials represent an ideal pathophysiological model more than a real patient, as they are young, nonsmoker, without concomitant diseases, without the need for multiple drug regimens. A recently published comparative analysis of mepolizumab studies highlighted a number of differences between the real-life and clinical trials study populations. Overall, the real-world patients were older, presented a higher blood eosinophils level and more frequently suffered from nasal polyposis, whereas the clinical trial population showed a worse pulmonary function and the need of a higher OCS dose at baseline [17].

Similar differences in comparison with clinical trials [7–9,11] were observed in our study population as well; the patients' average age was 54.5 years, age range 21.1–80.5 years, mean blood eosinophils level (cells/μL) was 983 ± 102, nasal polyposis was detected in 42 subjects (60.9%). On the other hand, mean lung function was better than in clinical trials (FEV% 73.1 ± 18.9) and the baseline OCS dose was lower (8.5 ± 8.8 mg).

Up to now few studies provided real-world evidence concerning mepolizumab efficacy and safety [18–20]. A small single center Italian study including 14 patients documented that a 6 months mepolizumab treatment was able to significantly decrease blood eosinophil levels, asthma exacerbation rate, OCS intake, and to improve symptoms control and lung function, showing a very good safety and tolerability profile [18]. A German study including 42 patients, assessed at baseline and 6 months after the treatment start, reported that mepolizumab was effective in 76% of them, in terms of lung function, blood eosinophils, and patient reported outcomes. However, no one of the baseline patients' characteristics (gender, BMI, smoking history, allergies, baseline level of

eosinophils) was able to predict treatment response [19]. A Japanese prospective open-label study on 32 patients demonstrated the long-term safety and efficacy of mepolizumab over a period of 48 weeks, including both clinical and biological markers of efficacy (ACT, FEV1%, eosinophils, plasma thymus, and activation-regulated chemokines) [20].

Overall, similarly to the other observational studies, our findings confirm that mepolizumab in the real-life setting as well is able to reduce the need of oral steroids, to improve patient reported outcomes (ACT), to increase lung function and to decrease the exacerbation rate. The most striking observation in our study is about the fast clinical response, which involves each one of the considered parameters. In fact, in comparison with baseline, at the first month assessment blood eosinophils count, ACT and FEV1% of predicted significantly changed. This finding is in line with the results described by another real-life study, which is the only one providing a first-month assessment of the same variables, though including an extremely smaller study population sample (14 patients) [18].

On the opposite, FeNO showed a statistically significant reduction only at the six months assessment. In patients treated with mepolizumab, a lack of parallelism between blood eosinophilia and FeNO or induced sputum eosinophilia values has been described [21,22]. Providing an explanation for that is not easy. In the light of FeNO as an expression of tissue eosinophilia, although controversial [23–25], its slow decrease may indicate that tissue inflammation is characterized by a different timing of response to mepolizumab in comparison with blood eosinophilia. On the other side it is known that IL-13 more than IL-5 drives FeNO production, which would be in this case partially independent from eosinophils. Also, many other factors may impact on FeNO levels, including infectious and environmental triggers that can sustain a TH2 inflammation beyond eosinophils in predisposed individuals [25,26]. No data on the trend of FeNO during mepolizumab treatment are available from the other real-life studies [18–20].

Furthermore, beside the first month assessment, a slightly dishomogeneous trend can be described for the different parameters during the study time frame. In fact, the initial blood eosinophil depletion at the first month follow-up remained unchanged over the whole observation period. ACT, although showing the greatest improvement between baseline and the first month follow-up, kept increasing at every follow-up time point. FEV1%, whose increase although statistically significant reached normal values in no more than half of patients, showed an evident improvement at the first month assessment, but no further noteworthy changes were observed at the 3 and 6 months follow-up assessments. A similar trend is reported by the small Italian real-life study [18]. It could be hypothesized that a lung function improvement after the first month since the start of the treatment is unlikely. However, the most important outcomes under a clinical perspective are represented by the reduction of OCS dose and of exacerbation rate, as they have the most relevant implications in patients' life and disease management. Similarly to other chronic diseases, the regular and/or high-dose intake of oral steroids in severe asthmatic patients is responsible for great impairment in terms of OCS-related adverse events and comorbidities [27,28]. In our study population, a dramatic decrease of OCS use has been recorded (Table 3). Similar observations are provided by other real-life studies, although including smaller study population samples [18–20].

The potential impact of nasal polyps, which represents a not negligible comorbidity in our dataset, on mepolizumab efficacy was also investigated. Similar patterns of improvement in terms of ACT score and blood eosinophils count could be observed among patients with and without nasal polyps. Of note, the baseline FEV1% was worse among asthma patients without polyps, who appeared more responsive to mepolizumab in terms of lung function. It can be hypothesized that the presence of nasal polyps increases the need for OCS intake, which may be related to the better baseline lung function in patients with polyposis. However, no other reports have so far specifically addressed the issue in real life.

Taken together, the body of real-life evidence remarks that the overall clinical outcome of the biologic treatment depends on a number of determinants including duration of the disease, current or previous smoking habit, presence of comorbidities, lung function status before the treatment start. Accordingly, the clinical response evaluation, as well as the decision about the treatment continuation, should be tailored on the specific patient background.

The small study population size represents a major limitation of our study. Due to the relatively low prevalence of severe asthma [29], a large sample of patients undergoing a specific biologic treatment is not easy within a real-life frame, especially when considering drugs that have been recently marketed. On the other hand, the relevance of real-world data in order to confirm and implement the outcomes emerging from the clinical trials has been described, as discussed before. Moreover to the best of our knowledge, our study includes up to now the largest population treated with mepolizumab for severe eosinophilic asthma in a real-life setting. The homogeneity of our population study, coming from a well-defined area in the Northeast of Italy, and the standardization of the clinical information collected within the RINOVA Network by referral centers sharing the same approach in the management of severe asthma, whether Allergy or Respiratory Medicine Units, in accordance with the strict recommendations about the issue provided by the regional regulatory agency, is in our opinion an added value in providing real-world evidence about the effect of a biologic drug. Although the retrospective design of the study could itself weaken our findings. Furthermore, when evaluating the asthma exacerbation rate, we compared the 12 months period before the mepolizumab treatment start with the 6 months period after it. However, although not completely correct from a methodological point of view, it corresponds to clinical practice setting. In fact, according to the Italian Regulatory Agency, the exacerbation rate in the previous 12 months has to be assessed as a prescription criterion for mepolizumab, while a 6 months follow-up evaluation is required in order to decide about the treatment continuation [30]. The same method has been also applied in another real-life study [19].

5. Conclusions

Our study, up to now including the largest population in real life, provided real-world evidence of mepolizumab safety, efficacy, and rapid clinical effect. The different timing and entity of clinical change of the considered parameters suggests that the definition of responder or nonresponder to the treatment should include a global evaluation and should be tailored according to each patient's profile. In fact, the greatest clinical change in terms of FEV1 and ACT in comparison with the baseline values was observed within the first month after the treatment start, suggesting that treatment continuation in patients without a clinical (lung function and patient reported outcomes) response within the first month should be carefully evaluated. On the other hand, if the steroid sparing effect and the reduction of exacerbation rate represent the most expected clinical outcomes for that patient, the impact of mepolizumab should be evaluated over a 6 months treatment frame.

However, further real-life research is needed especially to investigate the current unmet needs including the identification of treatment response predictors and the optimal treatment duration.

Funding

This paper was not funded.

Declaration of interest

The authors have no relevant affiliations or financial involvement with any organization or entity with a financial interest in or financial conflict with the subject matter or materials discussed in the manuscript. This includes employment, consultancies, honoraria, stock ownership or options, expert testimony, grants or patents received or pending, or royalties.

Reviewer disclosures

Peer reviewers on this manuscript have no relevant financial or other relationships to disclose.

Author contributions

MC, GS, and AV conceived the study design and drafted the manuscript. LC provided the statistical analysis. FCB, GF, MRM, CM, FM, and ST contributed to collection, analysis, and interpretation of the data. All the authors critically revised the manuscript for intellectual content and finally approved the version to be published. All the authors agree to be accountable for all aspects of the work.

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References

Papers of special note have been highlighted as either of interest (•) or of considerable interest (••) to readers.

1. To T, Stanojevic S, Moores G, et al. Global asthma prevalence in adults: findings from the cross-sectional world health survey. BMC Public Health. 2012;19(12):204.
2. Chung KF, Wenzel SE, Brozek JL, et al. International ERS/ATS guidelines on definition, evaluation and treatment of severe asthma. Eur Respir J. 2014;43:343–373.

•• **It represents the international reference document for assessment and management of severe asthma.**

3. Humbert M, Busse W, Hanania NA, et al. Omalizumab in asthma: an update on recent developments. J Allergy Clin Immunol Pract. 2014;2:525–536.
4. Bagnasco D, Caminati M, Ferrando M, et al. Anti-IL-5 and IL-5Ra: efficacy and safety of new therapeutic strategies in severe uncontrolled asthma. Biomed Res Int. 2018 Nov 5;2018:5698212.
5. Haldar P, Brightling CE, Hargadon B, et al. Mepolizumab and exacerbations of refractory eosinophilic asthma. N Engl J Med. 2009;360:973–984.
6. Nair P, Pizzichini MM, Kjarsgaard M, et al. Mepolizumab for prednisone-dependent asthma with sputum eosinophilia. N Engl J Med. 2009 Mar;5(360):985–993.
7. Pavord ID, Korn S, Howarth P, et al. Mepolizumab for severe eosinophilic asthma (DREAM): a multicentre, double-blind, placebo-controlled trial. Lancet. 2012;380:651–659.
8. Ortega HG, Liu MC, Pavord ID, et al. MENSA investigators. Mepolizumab treatment in patients with severe eosinophilic asthma. N Engl J Med. 2014;371:1198–1207.
9. Bel EH, Wenzel SE, Thompson PJ, et al. SIRIUS investigators. Oral glucocorticoid-sparing effect of mepolizumab in eosinophilic asthma. N Engl J Med. 2014;371:1189–1197.
10. Lugogo N, Domingo C, Chanez P, et al. Long-term efficacy and safety of mepolizumab in patients with severe eosinophilic asthma: a multi-center, open-label, phase IIIb study. Clin Ther. 2016 Sep;38(9):2058–2070.e1.
11. Chupp GL, Bradford ES, Albers FC, et al. Efficacy of mepolizumab add-on therapy on health-related quality of life and markers of asthma control in severe eosinophilic asthma (MUSCA): a randomised, double-blind, placebo-controlled, parallel-group, multicentre, phase 3b trial. Lancet Respir Med. 2017 May;5(5):390–400.
12. Khatri S, Moore W, Gibson PG, et al. Assessment of the long-term safety of mepolizumab and durability of clinical response in patients with severe eosinophilic asthma. J Allergy Clin Immunol. 2018 Oct 23;S0091–6749(18):1742–1751.e7.
13. Saturni S, Bellini F, Braido F, et al. Randomized controlled trials and real life studies. Approaches and methodologies: a clinical point of view. Pulm Pharmacol Ther. 2014;27:129–138.
14. Caminati M, Senna G, Guerriero M, et al. Omalizumab for severe allergic asthma in clinical trials and real-life studies: what we know and what we should address. Pulm Pharmacol Ther. 2015;31:28–35.
15. Caminati M, Senna G, Chieco Bianchi F, et al. NEONET study group. Omalizumab management beyond clinical trials: the added value of a network model. Pulm Pharmacol Ther. 2014;29:74–79.
16. Mepolizumab EPAR. [cited 2019 Feb 20]. Available from: https://www.ema.europa.eu/en/medicines/human/EPAR/nucala
17. Bagnasco D, Milanese M, Rolla G, et al. The North-Western Italian experience with anti IL-5 therapy and comparison with regulatory trials. World Allergy Organ J. 2018 Dec 6;11(1):34.
18. Pelaia C, Busceti MT, Solina S, et al. Real life of the clinical, functional and hematologic effects of mepolizumab in patients with severe eosinophilic asthma: results of a single-centre observational study. Pulm Pharmacol Ther. 2018;53:1–5.
19. Drick N, Seeliger B, Welte T, et al. Anti-IL-5 therapy in patients with severe eosinophilic asthma – clinical efficacy and possible criteria for treatment response. BMC Pulm Med. 2018;18:119.
20. Kurosawa M, Sutoh E. Prospective open-label study of 48-week subcutaneous administration of mepolizumab in Japanese patients with severe eosinophilic asthma. J Investig Allergol Clin Immunol. 2019;29(1):40–45.
21. Ojanguren I, Chaboillez S, Lemiere C. Low blood eosinophil counts are not always a reliable marker of clinical response to

mepolizu- mab in severe asthma. J Allergy Clin Immunol Pract. 2018;30:S2213–S2198.
22. Caminati M, Vianello A, Chieco Bianchi F, et al. NEONET study group. Relevance of Th2 markers in the assessment and therapeutic management of severe allergic asthma: a real life perspective. J Investig Allergol Clin Immunol. 2019 Jan 24:1–22.
23. Caminati M, Senna G. Uncontrolled severe asthma: starting from the unmet needs. Curr Med Res Opin. 2018 Oct;29:1–3.
24. Pavlidis S, Takahashi K, Ng Kee Kwong F, et al. "T2-high" in severe asthma related to blood eosinophil, exhaled nitric oxide and serum periostin. on behalf of the U-BIOPRED study group. Eur Respir J. 2019 Jan 3;53(1):pii: 1800938.
- **This research paper provides an original insight on Th2 clinical biomarkers in severe asthma.**
25. Hoyte FCL, Gross LM, Katial RK. Exhaled nitric oxide: an update. Immunol Allergy Clin North Am. 2018 Nov;38(4):573–585.
26. Caminati M, Pham DL, Bagnasco D, et al. Type 2 immunity in asthma. World Allergy Organ J. 2018 Jun 26;11(1):13.
27. Sullivan PW, Ghushchyan VH, Globe G, et al. Oral corticosteroid exposure and adverse effects in asthmatic patients. J Allergy Clin Immunol. 2018;141:110–116.e7.
- **An important and extensive contribution concerning the impact of steroid treatment on asthma morbidity**
28. Barry LE, O'Neill C, Patterson C, et al. Age and sex associations with systemic corticosteroid-induced morbidity in asthma. J Allergy Clin Immunol Pract. 2018 Nov- Dec;6(6):2014–2023.e2.
29. Vianello A, Caminati M, Andretta M, et al. Prevalence of severe asthma according to the drug regulatory agency perspective: an Italian experience. World Allergy Organ J. 2019 May 10;12 (4):100032.
- **One of the few epidemiological papers on the prevalence of severe asthma, estimated by an objective tool.**
30. Italian regulatory agency dispositions about the use of nucala. [cited 2019 Feb 20]. Available from: http://www.gazzettaufficiale.it/eli/id/2017/02/28/17A01570/sg;jsessionid=GDAhkFaCP3aDv1A99QwQ__.ntc-as2-guri2a