

Accepted Manuscript

Analysis of the drop-out rate in patients receiving mepolizumab for severe asthma in real life

Carlo Lombardi, Diego Bagnasco, Cristiano Caruso, Mariella D'Amato, Francesco Menzella, Manlio Milanese, Gianenrico Senna, Giorgio Walter Canonica, Giovanni Passalacqua

PII: S1094-5539(18)30277-3

DOI: <https://doi.org/10.1016/j.pupt.2018.12.003>

Reference: YPUPT 1770

To appear in: *Pulmonary Pharmacology & Therapeutics*

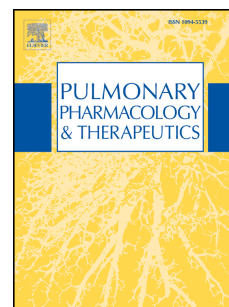
Received Date: 25 November 2018

Revised Date: 27 December 2018

Accepted Date: 28 December 2018

Please cite this article as: Lombardi C, Bagnasco D, Caruso C, D'Amato M, Menzella F, Milanese M, Senna G, Canonica GW, Passalacqua G, Analysis of the drop-out rate in patients receiving mepolizumab for severe asthma in real life, *Pulmonary Pharmacology & Therapeutics* (2019), doi: <https://doi.org/10.1016/j.pupt.2018.12.003>.

This is a PDF file of an unedited manuscript that has been accepted for publication. As a service to our customers we are providing this early version of the manuscript. The manuscript will undergo copyediting, typesetting, and review of the resulting proof before it is published in its final form. Please note that during the production process errors may be discovered which could affect the content, and all legal disclaimers that apply to the journal pertain.



1st revision**Analysis of the drop-out rate in patients receiving
Mepolizumab for severe asthma in real life**

**Carlo Lombardi MD¹, Diego Bagnasco MD², Cristiano Caruso MD³,
Mariella D'Amato MD PhD⁴, Francesco Menzella MD⁵, Manlio Milanese MD⁶,
Gianenrico Senna MD⁷, Giorgio Walter Canonica MD⁸,
Giovanni Passalacqua MD²**

- 1 Departmental Unit of Allergology & Pneumology, Fondazione Poliambulanza Hospital, Brescia;
- 2 Allergy & Respiratory Diseases, University of Genoa, Genoa;
- 3 Allergology Unit, Ospedale Complesso Integrato Columbus C.I.C. Rome;
- 4 Department of Pneumology, "Federico II University", AO "Dei Colli" Monaldi Hospital-Naples.
- 5 Unità Operativa di Pneumologia, Arcispedale Santa Maria Nuova, Azienda Ospedaliera di Reggio Emilia;
- 6 S.C. Pneumologia Pietra Ligure, ASL 2, Savona;
- 7 Servizio di Allergologia, Ente Ospedaliero-Universitario di Verona;
- 8 Personalized Medicine Center, Humanitas University, Milan

ITALY

Word count: 1.006

References: 13

Tables: 3

Correspondence:

Dr. Diego Bagnasco

Allergy and Respiratory Diseases

Pad Maragliano. L.go R.Benzi 10, 16132 Genoa, ITALY

IRCCS Ospedale Policlinico San Martino

University of Genoa- Italy

e-mail: dott.diegobagnasco@gmail.com

Funding and conflict of interest: none to declare for all Authors

ABSTRACT.

Mepolizumab (anti IL-5, monoclonal antibody) is commercially available in Italy since more than one year for the treatment of severe hypereosinophilic asthma. Its efficacy and safety were evaluated in several regulatory trials. The characteristics of this drug in real life began to be assessed only recently. We describe herein the drop-out rate observed with mepolizumab in real life, because this datum can indirectly reflect the safety and tolerability aspects. The demographic and clinical data of patients receiving mepolizumab for severe asthma were collected, and the number and reasons for discontinuation of the treatment were analyzed. The database involves 143 patients (67 male, age range 19-80 year) who received at least one dose of mepolizumab. The observed discontinuation rate was 6/143 (4.2%). Five out of 6 discontinuations were due to lack of response, and one was an adverse event (urticaria) probably related to the treatment. There was no clinical difference between the drop-out group and the patients still ongoing. As compared to the clinical trials published the discontinuation rate was lower in our population, especially for adverse events (7% vs 23.7%). Thus, the tolerability of mepolizumab, as derived from discontinuations, seems to be better in real-life than in clinical trials

KEY WORDS: mepolizumab; real-life: dropout; safety; severe asthma

INTRODUCTION

Severe asthma still represents a major challenge for all clinicians and a heavy burden from the socio-economical point of view. Severe asthma is usually defined, according to ERS/ATS guidelines, when the control of the disease cannot be reached despite the maximum standard therapy (1). Nowadays some advanced therapeutic approaches are available, namely anti IgE (Omalizumab), and IL-5 antagonists (Mepolizumab, Reslizumab and Benralizumab). Mepolizumab (MEP) was the first commercialized anti IL-5 treatment, thus a relatively large and evolving experience in the real-life setting is currently available. As for all chronic treatments, adherence remains pivotal, especially for such expensive therapies, thus a detailed analysis of drop outs would be extremely useful.

Indeed, according to the literature concerning Omalizumab (2) that is commercially available since more than 15 years, in clinical trials the drop-out rate ranges about between 7% and 20%. Although the reasons for withdrawal were not systematically reported in detail, patients' decision and adverse events were the most frequently reported causes. In real-life studies the drop-out rate ranged from 0 to 45.5 % and, usually, the lack of efficacy was responsible for discontinuation. According to NEONet data (2), 32 % of treated patients dropped out, with an increasing number of drop outs observed over time.

Since the real-life experience with MEP is growing, we attempted to carefully evaluate and analyze the drop-out rate in those patients prescribed with MEP itself for severe eosinophilic asthma according to prescription rules in some regions of Italy (Lombardia, Liguria, Lazio, Campania, Emilia Romagna and Veneto).

METHODS

Demographic, clinical and instrumental data (age, sex, exacerbations, pulmonary function, blood eosinophils) were collected starting from March 2017 (when MEP was commercialized), in 7 severe asthma centers, using a shared database. Also, the reason for discontinuation and the time elapsed from the first administration were assessed. In particular, the presence of at least 2 asthma exacerbations in the last year of follow-up was considered as treatment failure, and the algorithm proposed by Drick et al was applied (3). All patients provided their informed consent to the treatment and to the anonymous data management as per standard care procedures.

RESULTS

The current database involves 143 patients (67 male, age range 19-80). Out of those who received at least one dose of MEP, 6 (4,2%) dropped out (**Table 1**). Two were female and 4 were male, and their mean age was 62.7 years. As previously described the prevalence of nasal polyposis

was high in the whole treated population (52%), irrespective of dropouts (4). Main baseline and last assessment characteristics of persisting and drop-out population are summarized in **Table 1**.

The clinical response and drop out-rate was in general independent of the expected reduction in eosinophils (**Table 2**). Of note, 2 of the drop-out patients were also previously non responder to anti IgE treatment, that was correctly prescribed (pts 1 and 6), and one had been previously involved in a clinical trial with Dupilumab. The discontinuation of MEP was due to an adverse events in one single patient (1/143, 0,7% of patients): it was a generalized urticaria, with asthenia and arthralgias that occurred about 24 hours after the third MEP dosing. There were no other systemic signs (e.g. dyspnea, hypotension, angioedema, pulmonary function changes), and the blood chemistry tests remained normal. Symptoms resolved with oral antihistamine and corticosteroid within 48 hours. With the limits of a such small drop-out rate, the occurrence of the major comorbidities was not apparently different between dropouts (diabetes 4/6, 66.7%; rhinosinusitis 3/6, 50%) and patients still receiving the treatment (diabetes 110/137, 80% rhinosinusitis 61/137, 46%). Also, the occurrence of gastrooesophageal reflux, nasal polyposis and rhinosinusitis was similar in dropouts and those still persisting in MEP treatment (**TABLE 1**).

The discontinuations due to lack of efficacy (exacerbations) were strictly related to our National Healthcare System rules that require, for renewal of the prescription a disappearance/reduction in exacerbations. As compared to the published clinical trials the drop-out rate in real life was overall low (4.2%), and the discontinuation was due to adverse events in only 1/6 of drop-outs and 1/143 (0.7%) of patients. Only mild side effects were reported: headache (4 patients), mild local reaction at site injection, all of these spontaneously resolved within 1 hour, and without any drug administration.

DISCUSSION

MEP is effective in severe eosinophilic asthma, as confirmed in several randomized controlled trials (5-10). It reduces the rate of exacerbations, hospital admissions and improves the quality of life of patients, thus providing a socio-economical advantage. Nonetheless, in randomized trials, drop-outs (discontinuation of treatment) due to various reasons have been described. Looking at the available literature the drop-out ratio among the patients receiving MEP is about 9% (**Table 3**). This is in line with what previously described with Omalizumab for severe asthma (3). Few data are available in the real-life setting for Mepolizumab. Zhang et al. recently reported a drop-out rate of 6/30 (20%) patients (3 asthma worsening, 2 local reactions, 1 transitory ischemic attack) (11). In our database that includes more than 140 patients, followed for up for one year (time of commercial introduction of the drug in Italy), the drop-out rate was low (4.2%), and only 1 patient dropped out

122 for an adverse event (urticaria), not clearly attributable to the drug. In conclusion, in real-life, the
123 rate of drop-outs with MEP appears to be quite low and most often due to treatment failure rather
124 than to adverse events. Comorbidities were similar in those who dropped out and in those still on
125 treatment, and the same could be presumed for the side effects of systemic steroids. The population
126 is certainly small, as can be expected for such selected severe asthma patients, but the findings are
127 consistent with those previously published in clinical trials, especially concerning the safety profile
128 of the drug, that will be fully assessed only in the real-life setting (12, 13).

REFERENCES

1. Chung KF, Wenzel SE, Brozek JL, Bush A, Castro M, Sterk PJ, et al. International ERS/ATS guidelines on definition, evaluation and treatment of severe asthma. *Eur Respir J*. 2014;43: 343-73. ERS/ATS
2. Caminati M, Senna G, Stefanizzi G, Bellamoli R, Longhi S, Chieco-Bianchi F, et al. Drop-out rate among patients treated with omalizumab for severe asthma: Literature review and real-life experience. *BMC Pulm Med*. 2016; 16: 128.
3. Drick N, Seeliger B, Welte T, Fuge J, Suhling H. Anti-IL-5 therapy in patients with severe eosinophilic asthma - clinical efficacy and possible criteria for treatment response. *BMC Pulm Med*. 2018 Jul 18;18(1):119.
4. Bagnasco D, Milanese M, Rolla G, Lombardi C, Bucca C, Heffler E, et al. Anti-IL-5 therapy in real life. The North-Western Italian experience 3 and comparison with the regulatory trials. *World Allergy Organ J*. 2018 Dec 6;11(1):34
5. Pavord ID, Korn S, Howarth P, Bleecker ER, Buhl R, Keene ON, et al. Mepolizumab for severe eosinophilic asthma (DREAM): a multicentre, double-blind, placebo-controlled trial. *Lancet*. 2012; 380: 651-9
6. Ortega HG, Liu MC, Pavord ID, Brusselle GG, FitzGerald JM, Chetta A, et al. Mepolizumab treatment in patients with severe eosinophilic asthma. *N Engl J Med*. 2014; 371: 1198-207
7. Bel EH, Wenzel SE, Thompson PJ, Prazma CM, Keene ON, Yancey SW, et al. Oral glucocorticoid-sparing effect of mepolizumab in eosinophilic asthma. *N Engl J Med*. 2014; 371: 1189-97
8. Lugogo N, Domingo C, Chanez P, Leigh R, Gilson MJ, Price RG, 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;38(9):2058-2070
9. Chupp GL, Bradford ES, Albers FC, Bratton DJ, Wang-Jairaj J, Nelsen LM, 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; 5: 390-400
10. Haldar P, Brightling CE, Hargadon B, Gupta S, Monteiro W, Sousa A, et al. Mepolizumab and Exacerbations of Refractory Eosinophilic Asthma. *N Engl J Med*. 2009; 360: 973-984
11. Passalacqua G, Matucci A, Vultaggio A, Bagnasco D, Mincarini M, Maggi E, Canonica GW. The safety of monoclonal antibodies in asthma. *Expert Opin Drug Saf*. 2016; 15: 1087-95.
12. Khatri S, Moore W, Gibson PG, Leigh R, Bourdin A, Maspero J 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 22. doi: 10.1016/j.jaci.2018.09.033. [Epub ahead of print]
13. Farne HA, Wilson A, Powell C, Bax L, Milan SJ. Anti-IL5 therapies for asthma. *Cochrane Database Syst Rev*. 2017 Sep 21;9:CD010834

Table 1 : main characteristics of patients still persisting in therapy and those dropped out at the last administration of mepolizumab.

	Persisting patients	Drop Out	P-value
Number	137	6	-
Age, mean (range)	19-80	55-77	-
Male, N (%)	74 (54)	2 (33)	-
Nasal Polyps, N (%)	72 (53%)	2 (33%)	.0001
Rhinosinusitis (%)	61 (44%)	3 (50%)	.52
Diabetes (%)	110 (80%)	4 (67%)	.45
Eosinophils at baseline, mean (SD)	737 (396)	755 (273)	.794
Eosinophils at last assessment, mean (SD)	113 (90)	150 (62)	.167
FEV ₁ % at baseline, mean (SD)	72 (20)	67 (9)	.418
FEV ₁ at last assessment, mean (SD)	80 (18)	69 (8)	.084
ACT at baseline, mean (SD)	18 (4)	12 (3)	.397
ACT at last assessment, mean (SD)	23 (2)	14 (3)	.001
Exacerbations at baseline, mean (SD)	4.1 (2.8)	2.5 (1.3)	.246
Exacerbations at last assessment, mean (SD)	0.6 (1.1)	2.2 (0.7)	.002

Table 2: Characteristics of drop-out recorded (6/143) in the current real-life database**(patients on Mepolizumab 100 mg subcutaneously/month)**

P T	Age	sex	Age at onset (YRS)	Smoking status (Y N, ex)	ACT baseline	ACT at drop out	FEV ₁ % baseline	FEV ₁ at Drop out	Baseline eos /mm ³	Current eos /mm ³	Exacerbations N/12 months	Exacerbations at drop out	Hospital admissions N/12 months	Hospital Admissions at drop out	Nasal polypsis Y/N	Other co- morbidities *	Doses at drop out	Cause of drop out
1	67	F	47	N	8	<u>10</u>	60	<u>62</u>	900	180	3	<u>2</u>	<u>0</u>	<u>0</u>	N	Osteoporosis Rhinosinusitis	12	Non responder
2	55	M	45	ex	9	<u>11</u>	66	<u>68</u>	1,200	200	2	<u>3</u>	<u>0</u>	<u>0</u>	Y	Diabetes, AH, Rhinosinusitis	13	Non responder
3	55	M	32	ex	15	<u>15</u>	67	<u>70</u>	720	61	0	<u>1</u>	<u>0</u>	<u>0</u>	N	NONE	3	Urticaria
4	77	F	41	N	10	<u>13</u>	68	<u>72</u>	850	220	3	<u>2</u>	<u>1</u>	<u>0</u>	N	Diabetes, AH obesity, GERD	7	Non responder
5	55	M	40	ex	15	<u>17</u>	55	<u>58</u>	370	170	4	<u>2</u>	<u>1</u>	<u>0</u>	N	Osteoporosis, AH, obesity, diabetes, GERD	6	Non responder
6	67	M	60	ex	17	<u>18</u>	84	<u>85</u>	490	70	3	<u>3</u>	<u>0</u>	<u>0</u>	Y	Osteoporosis, diabetes, GERD, Rhinosinusitis	12	Non responder

*AH: arterial hypertension; GERD: Gastroesophageal reflux disease

Table 3: Drop-out and reasons reported in the Randomized Controlled Trials and in current population in patients actively treated with Mepolizumab. The dose was 100 mg subcutaneously other than in an arm about Ortega study (6).

Author (ref)	N pts active	Durat. (mths)	Mean age	M/F %	Total Drop out N (%)	Reasons for dropout N and % in treated patients			
						Personal Decision N (%)	Lack of efficacy N (%)	Adverse Events N (%)	Other/not defined N (%)
Pavord (5)	462	12	49.4	37/63	68 (14.7)	17 (25)	14 (21)	22 (32)	15 (22)
Ortega (6)	385	8	50.5	42/58	25 (6.5)	0	3 (12)	1 (4)	21 (84)
75 mg IV	191		50	45/55	16 (8)		1 (6.2)	0	15 (93.8)
100 mg SC	194		51	40/60	9 (5)		2 (22)	1 (11)	6 (67)
Bel (7)	69	8	50	36/64	3 (4.3)	0	0	3 (100)	0
Lugogo (8)	651	12	51	45/55	66 (10.1)	14 (21)	19 (29)	19 (29)	22 (33)
Chupp (9)	276	6	49.8	46/54	5 (1.8)	2 (40)	0	2 (40)	1 (20)
Haldar (10)	29	12	48	48/52	2 (6.9)	0	0	1 (50)	1 (50)
Total* in Clinical trials	1,872	9.2	49.8	42/58	169 (9)	33 (19.5)	36 (21.3)	49 (23.7)	60 (36.5)
Current database	143	8.5	67.1	36/67	6 (4.2)	0	5 (3.5)	1 (7)	0

1: 75 mg intravenous/4 weeks; 2: 100 mg subcutaneous/4 weeks; * overall mean