International Archives of Allergy and Immunology

Clinical Allergy – Brief Report

Int Arch Allergy Immunol 2020;181:613–617
DOI: 10.1159/000508559

Received: April 20, 2020
Accepted: May 8, 2020
Published online: June 22, 2020

Mepolizumab in Severe Eosinophilic Asthma: A 2-Year Follow-Up in Specialized Asthma Clinics in Greece: An Interim Analysis

Maria Kallieri[a] Eleftherios Zervas[b] Konstantinos Katsoulis[c] Eva Fouka[d] Konstantinos Porpodis[d] Konstantinos Samitas[b] Andriana I. Papaioannou[a] Maria Kipourou[c] Eleni Gaki[e] Stylianos Vittorakis[f] Miltiadis Markatos[f] Katerina Dimakou[g] Sevasti Ampelioti[g] Sofia Koukidou[g] Michael Makris[h] Maria Ntakoula[h] Marija Hadji Mitrova[d] Konstantinos Glynos[i] Katerina M. Antoniou[j] Mina Gaga[b] Nikolaos Tzanakis[j] Katerina Markopoulou[k] Despoina Papakosta[d] Petros Bakakos[l] Stelios Loukides[a]

[a]2nd Respiratory Department, Attiko University Hospital, National and Kapodistrian University of Athens Medical School, Athens, Greece; [b]Sotiria Sotiria 7th Department, Athens Chest Hospital, Athens, Greece; [c]Respiratory Department, 424 Army General Hospital, Thessaloniki, Greece; [d]Pulmonary Department, Aristotle University of Thessaloniki, Thessaloniki, Greece; [e]Private Practice, Trikala, Greece; [f]Private Practice, Chania, Greece; [g]5th Respiratory Clinic, "Sotiria" Chest Hospital, Athens, Greece; [h]Allergy Unit, 2nd Department of Dermatology and Venereology, Attikon University General Hospital, Athens, Greece; [i]GSK Medical Division Greece, Athens, Greece; [j]Respiratory Medicine Department, University Hospital of Heraklion, Iraklio, Greece; [k]1st Pulmonary Department, Papanikolaou General Hospital Thessaloniki, Thessaloniki, Greece; [l]1st Respiratory Department, Sotiria Chest Hospital, National and Kapodistrian University of Athens Medical School, Athens, Greece

Keywords
Severe asthma · Mepolizumab · Real life · Biologics · Eosinophils

Abstract
Introduction: Mepolizumab is a monoclonal antibody against IL-5 for the treatment of severe eosinophilic asthma. The aim of the current study was to present a predesigned interim analysis of the data of patients who have completed 1 year of therapy with mepolizumab. ***Methods:*** This study is a prospective multicenter, noninterventional 2-year observational study and aims to describe the clinical benefit and safety profile of mepolizumab in patients with severe eosinophilic asthma. ***Results:*** Compared to the year preceding the initiation of treatment, the annual rate of exacerbations decreased significantly, from 4.3 ± 2.3 to 1.3 ± 1.8; $p < 0.0001$. Forty-two patients received maintenance dose of oral corticosteroids (OCS) at baseline. From these patients at the end of 1 year of therapy with mepolizumab, 17 patients (40%) had achieved OCS discontinuation. A reduction in the median dose of OCS was also achieved. After 1 year of treatment with mepolizumab, the asthma control test score significantly increased from 16.3 ± 3.7 to 21.2 ± 3.8 ($p < 0.0001$). This marked clinical improvement was paralleled by a significant reduction of blood eosinophil count. All patients showed a considerable improvement of airflow limitation. In respect to adverse events of treatment with mepolizumab, 19 patients (27%) were recorded to have at least one such occurrence during their 1-year treatment. ***Conclusions:*** We have shown that in patients with severe eosinophilic asthma, 1

Edited by: H.-U. Simon, Bern.

karger@karger.com
www.karger.com/iaa

Stelios Loukides
2nd Respiratory Department, Attiko University Hospital
National and Kapodistrian University of Athens Medical School
Smolika 2, GR–16673 Athens (Greece)
loukstel@med.uoa.gr

year of treatment with mepolizumab was safe, resulted in significant reduction of the annual exacerbation rate, reduction (or even discontinuation) of the needed dose of OCS, and improvements of asthma control and lung function.

Introduction

Eosinophils have been identified as suitable drug targets in multiple eosinophilic diseases [1]. The latest GINA recommendations suggest the use of mepolizumab as an add-on treatment for patients with severe eosinophilic asthma [2]. Mepolizumab is an IgG1/k class-humanized monoclonal antibody which blocks circulating interleukin-5 (IL-5) which is responsible for the development, maturation, and survival of eosinophils [3]. Several randomized controlled trials have shown the efficacy and safety of mepolizumab in patients with severe eosinophilic asthma [4–6]; however, to date, only a few studies have shown its effectiveness in a real-life setting [7–9]. We are currently running a real-life, 2-year follow-up study exploring the effects of mepolizumab in patients with severe eosinophilic asthma in Greece. The aim of the current study was to present a predesigned interim analysis of the data of patients who have completed 1 year of therapy with mepolizumab.

Methods

This study is a prospective multicenter, non-interventional observational study. It is conducted in several centers in Greece for a 2-year time period and aims to describe patient characteristics, medical history, the clinical benefit, and safety profile of mepolizumab in patients with severe eosinophilic asthma newly initiated to the drug. The study will include approximately 140 patients (and is currently fully enrolled) and is expected to be completed on December 2020.

Primary end point is the reduction of the annual rate of asthma exacerbations. Secondary end points include alterations in asthma control test (ACT), pulmonary function (using simple spirometry), reduction of the dose of oral corticosteroids (OCS) (for patients who received this treatment at baseline), and alterations in the number of blood eosinophils. Analytical methods and statistical analysis are provided as an online supplement.

Results

Eighty-seven patients were initially screened and followed up. Out of the baseline 87 patients, 70 were included in the interim analysis. The flow chart of the study participants is shown in online suppl. Fig. E1; see www.karger.com/doi/10.1159/000508559 for all online suppl. material. Subjects' characteristics are summarized in Table 1. Compared to the year preceding the initiation of treatment, the annual rate of exacerbations decreased sig-

Table 1. Demographic and baseline functional characteristics of the study participants

Variables	Recruited patients (n = 140)	Patients for the interim analysis (n = 70)	Excluded patients (n = 17)
Age	56±13	55±12	52±111
Gender (M/F)	52/88	22/48	6/11
BMI kg/m^2	28±7	29±6.5	27±7
Smoking habit (current smokers/ex-smokers/never smokers)	9/23/108	0/11/59	0/0/17
Pack years (median (CI))	10 (1.30)	8 (1.27)	ND
Years with asthma	18±14	20±13	17±13
Atopy, n	76	35	8
Blood eosinophils AC	703±537	661±456	598±397
FEV_1, % pred	68±20	67±17	72±17
FEV_1/FVC %	65±14	63±18	66±13
ACT	16±4.5	16±3.5	15±4
Number of exacerbations in the previous year	4±2	4.5±2	4±2
Treatment with OCS (n/daily dose in mg)	6,611±8	4,210±7	87.5±4
LAMA/LTRAs, n	54/39	38/11	4/9
Prior therapy with omalizumab, n (%)	63 (45)	30 (43)	6 (36)

Data are presented as mean ± SD unless otherwise indicated. AC, absolute count; ACT, asthma control test; CI, confidence intervals; F, female; FEV_1, forced expiratory volume in 1 s; FVC, forced exhaled vital capacity; LAMA, long-acting muscarinic antagonists; LTRAs, leukotriene receptor antagonists; M, male; ND, not done; OCS, oral corticosteroids.

nificantly, from 4.3 ± 2.3 to 1.3 ± 1.8; $p < 0.0001$, a 70% reduction (Fig. 1a). Interestingly, the annual rate of exacerbations was even greater in patients with greater numbers of blood eosinophils (online suppl. Fig. E2). Forty-two patients received maintenance dose of OCS at baseline. From these patients, 8 (20%) achieved total discontinuation at 4 months of follow-up, 15 (30%) at 8 months of follow-up, and at the end of 1 year of therapy with mepolizumab, totally 17 patients (40%) had achieved OCS discontinuation (online suppl. Fig. E3). A reduction in the median dose of OCS was also achieved after 1 year of treatment with mepolizumab from 10.1 ± 7.0 to 4.5 ± 6.1 (mg of prednisolone or equivalent), $p < 0.0001$ (56% reduction) (Fig. 1b). After 1 year of treatment with mepolizumab, the ACT score significantly increased from 16.3 ± 3.7 to 21.2 ± 3.8 ($p < 0.0001$) (Fig. 1c). This marked clinical improvement was paralleled by a significant reduction of blood eosinophil count, which dropped from 661.3 ± 456.33 cells/μL to 108.9 ± 96.13 ($p < 0.0001$). All patients showed a considerable improvement of airflow limitation, demonstrated by enhancements of both FEV_1 % pred and FEV_1/FVC ratio, which increased from 67.3 ± 17.2 to 74.3 ± 18.0, $p < 0.0001$ (10.4% increase) and from 63.5 ± 18.2 to 67.0 ± 13.5, $p < 0.01$ (4.7% increase),

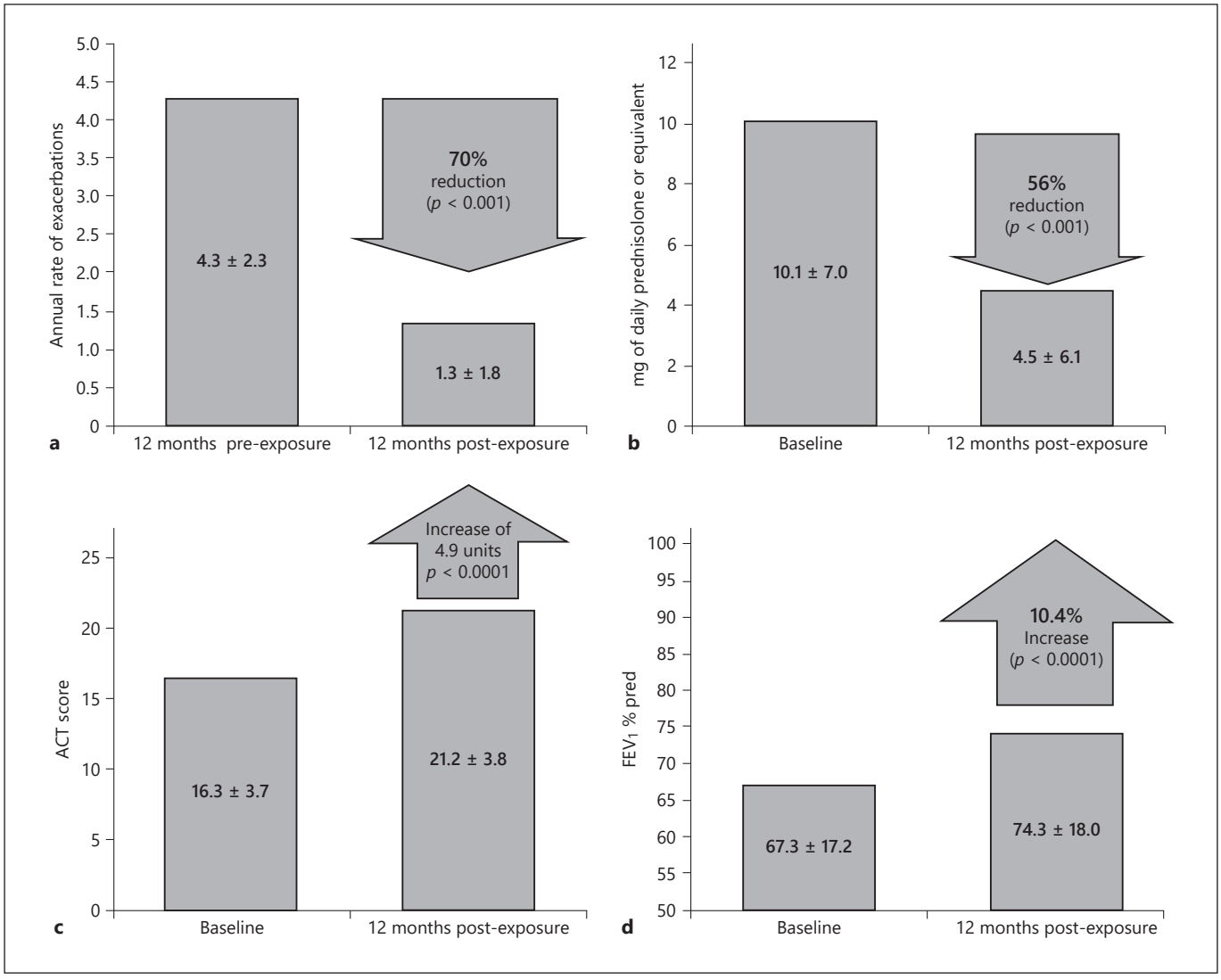

Fig. 1. a Reduction in the annual exacerbation rate after 1 year of therapy with mepolizumab. **b** Reduction of OCS dose after 1 year of therapy with mepolizumab. **c** Improvement in ACT after 1 year of therapy with mepolizumab. **d** FEV_1 % pred improvement after 1 year of therapy with mepolizumab. For data, see text. ACT, asthma control test; FEV_1, forced expiratory volume in 1 s; OCS, oral corticosteroids.

respectively (Fig. 1d). With respect to adverse events of treatment with mepolizumab, 19 patients (27%) were recorded to have at least one such occurrence during their 1-year treatment. Online suppl. Table E1 in the online supplement shows the kind of adverse event recorded, as well as their frequency.

Discussion

In this multicenter observational study, we have shown that in patients with severe eosinophilic asthma, 1 year of treatment with mepolizumab was safe, resulted in significant reduction of the annual exacerbation rate, reduction (or even discontinuation) of OCS, and improvements of asthma control and lung function. In our study, mepolizumab resulted in an approximately 70% reduction in the annual exacerbation rate compared to the year prior the initiation of treatment. This reduction was much greater compared to RCTs [5, 10] in which exacerbation reduction was 53 and 58%, respectively. Additionally, when examining exacerbation reduction according to the number of blood eosinophils, still in our study, the annual rates of exacerbation are also lower compared to RCTs since we have observed a 71% reduction in patients with ≥300 cells/μL and a 72% reduction in patients with ≥400 cells/μL which are greater compared to the 59 and 66%, respectively, which were observed in the pooled analysis of the 2 main approval studies MENSA and DREAM [6]. In our study, the use of mepolizumab resulted in significant reduction of the need of OCS and in many cases has resulted in their discontinuation, an important increase in FEV_1 which augmented approximately 10.4% from baseline and finally a significant improvement in ACT score of approximately 4.9 units which is greater than the minimally clinical important difference. It is important to mention that unlike RCTs, dose reduction and discontinuation of OCS was not based in any specific algorithm [11] but was performed according to the guidance of the treating physician. For this reason, one can hypothesize that probably some patients might be able to reduce further or even discontinue OCS. The clinical significance of improvement in lung function still remains controversial since it still has to be determined whether this improvement in lung function will be maintained in a real-life setting. However, in our study, we showed an amelioration in airflow limitation which is probably attributed to the fact that the majority of our patients were characterized by persistent airflow limitation. As for the ACT, our observation is also in accordance to other real-life studies of the use of mepolizumab [7] in severe eosinophilic asthma and remains to be addressed if this clinically significant improvement of asthma control will be also persistent. Importantly, there were no safety concerns related to the use of mepolizumab in our study. This is also an important observation since unlike RCTs, patients were nonselected in the setting of comorbidities or concurrent medication use.

In conclusion, in a real-life setting of patients with severe eosinophilic asthma, treatment with mepolizumab was associated with a significant reduction in the annual rate of exacerbations, along with significant improvements in asthma control and lung function and reduction in OCS use. These effects were of an order that was clinically important and aligned with the randomized controlled trials of mepolizumab in severe asthma.

Statement of Ethics

All participants signed an informed consent. The study was approved from all local ethic committees, and all patients provided oral and written informed consent. The study was registered in clinical trials.gov: ClinicalTrials.gov Identifier: NCT04084613.

Disclosure Statement

All authors have no conflicts of interest to disclose. GSK provided a grant for the statistical analysis. Konstantinos Glynos is a GSK employee.

Authors Contributions

All authors from different centers recruited and followed up patients. Preselected data were recorded for each patient as stated in the methods section. Additionally, Prof. Loukides was also responsible for the overall content of the manuscript as guarantor. Prof. Bakakos: writing – review & editing and supervision. Andriana Papaioannou: writing – review & editing. Konstantinos Glynos from GSK provided statistical analysis.

References

1 Simon HU, Yousefi S, Germic N, Arnold IC, Haczku A, Karaulov AV, et al. The cellular functions of eosinophils: collegium internationale allergologicum (CIA) update 2020. Int Arch Allergy Immunol. 2020;181(1):11–23.

2 Global Initiative for Asthma. GINA workshop report, Global strategy for Asthma Management and prevention. Revised 2019. Available on http://www.ginasthma.org 2019.

3 Cosmi L, Maggi L, Mazzoni A, Liotta F, Annunziato F. Biologicals targeting type 2 immunity: lessons learned from asthma, chronic urticaria and atopic dermatitis. Eur J Immunol. 2019 Sep;49(9):1334–43.
4 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 Aug 18;380(9842):651–9.
5 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 Sep 25;371(13):1198–207.
6 Ortega HG, Yancey SW, Mayer B, Gunsoy NB, Keene ON, Bleecker ER, et al. Severe eosinophilic asthma treated with mepolizumab stratified by baseline eosinophil thresholds: a secondary analysis of the DREAM and MENSA studies. Lancet Respir Med. 2016 Jul;4(7):549–56.
7 Pelaia C, Busceti MT, Solinas S, Terracciano R, Pelaia G. Real-life evaluation of the clinical, functional, and hematological effects of mepolizumab in patients with severe eosinophilic asthma: results of a single-centre observational study. Pulm Pharmacol Ther. 2018 Dec;53:1–5.
8 Bagnasco D, Caminati M, Menzella F, Milanese M, Rolla G, Lombardi C, et al. One year of mepolizumab. Efficacy and safety in real-life in Italy. Pulm Pharmacol Ther. 2019 Oct;58:101836.
9 Pertzov B, Unterman A, Shtraichman O, Shitenberg D, Rosengarten D, Kramer M. Efficacy and safety of mepolizumab in a real-world cohort of patients with severe eosinophilic asthma. J Asthma. 2019 Sep;56:1–6.
10 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 May;5(5):390–400.
11 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 Sep 25;371(13):1189–97.