Exacerbation Rate Reduction with Mepolizumab, Stratified by Maintenance OCS Use and Eosinophil Levels. A Post-Hoc Analysis of DREAM and MENSA Studies

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Severe asthma patients often have complex treatment requirements, due to the high burden of the disease, leading in 30-40% of them to require maintenance oral corticosteroids (OCS). Several biologic therapies recently approved for severe asthma have become the most appropriate steroid sparing strategy, when added to standard of care. Mepolizumab is a humanized monoclonal antibody against IL-5, licensed for the treatment of severe eosinophilic asthma (SEA). [1,2]

The benefit of mepolizumab in reducing exacerbations and in reducing oral corticosteroids has been proven in randomized controlled clinical trials, and in more recent real-life studies.[2]

Specifically, findings from two large trials of the clinical development program of mepolizumab [DREAM; NCT01000506] [1] and [MENSA; NCT01691521][3], have shown clinically significant reductions in asthma exacerbation rates after treatment with mepolizumab, compared with placebo, in patients with severe eosinophilic asthma (SEA). Furthermore, the clinical benefit of mepolizumab in reducing oral corticosteroid doses was demonstrated in the SIRIUS OCS sparing study (Oral Glucocorticoid-Sparing Effect of Mepolizumab in Eosinophilic Asthma Study) [4]. Modelling analysis in the DREAM study identified blood eosinophil counts as a predictor of treatment response to mepolizumab; hence, severe asthma patients were selected afterwards in the

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subsequent MENSA study on the basis of their blood eosinophil counts to comply the eosinophilic phenotype criterion.

The search for new biomarkers of early response to biologicals in severe asthma is ongoing, and in some studies the use of maintenance OCS has been proposed as a potential predictor of response. In a recent post-hoc analysis by Bleecker et al., the OCS maintenance dose predicted benralizumab efficacy in terms of reduction of exacerbations and FEV_1 improvement[5].However, the influence of OCS use on blood eosinophil levels is well-known, and their use, as a maintenance treatment, makes it difficult to establish a common threshold to define eosinophilia. This is why we believe it is necessary to evaluate the efficacy of biological therapies in relation to OCS use, but also, to blood eosinophil levels[6].

We aim to assess the influence of OCS maintenance use on exacerbation rate reduction with mepolizumab in severe eosinophilic asthma patients and stratified by baseline blood eosinophil levels.

For that purpose, post-hoc analysis was performed using the exacerbation data from the DREAM (N=616, mepolizumab doses 75mg IV, 250mg IV and 750mg IV) and MENSA (N=576, mepolizumab doses 75mg IV and 100mg SC) studies, which included overall188 (31%) and 144 (25%) patients in each study, respectively, that were on baseline maintenance OCS. To be included in this post-hoc analysis subjects were required to have baseline data on eosinophil levels and OCS maintenance use. Patients were excluded if they had baseline blood eosinophil levels< 150 cells/µL.

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Finally, the patients included in this analysis were divided into eight groups, according to their baseline eosinophil levels (cells/µL)on one hand(>=150-300, >=300-500, ≥500, all patients, i.e. 4 groups), and according to the OCS maintenance use (Yes/No) on the other (see table 1).

Statistical analysis

In order to model the response variable due to the dispersion of the data, the exacerbation rates have been analyzed using a negative binomial regression model, using the SAS Software. Explanatory covariates included treatment group; exacerbations in the year prior to the study (as an ordinal variable), baseline percentage of predicted forced expiratory volume in the first second (FEV1), study, region, and logarithm of time on treatment as an offset variable This model was fitted for the eight subgroups based on the baseline eosinophil levels and the OCS baseline maintenance therapy as defined in methods.

Of the 1192 patients included in the DREAM and MENSA studies, 920 subjects had blood eosinophil levels >=150 cells/ul (analysis population) and were eventually included in this post-hoc analysis; 278 of them received placebo and 642 mepolizumab.

Demographic characteristics were similar in both studies and in the analysis population Exacerbation rate reductions with mepolizumab were similar between OCS-treated patients (n=243) and patients without OCS treatment (n=677) in the analysis population. Results show greater reductions at higher baseline eosinophil counts(see also table 1, groups 3>2>1, and group 7>6>5 respectively), maintained in both the total and disaggregated analyses; while the response to mepolizumab in reducing the number of

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exacerbations appears not to be influenced by baseline OCS treatment (ratios in groups 4 and 8 are similar).

Several analyses evaluating the influence of OCS maintenance use on mepolizumab clinical benefit in terms of reducing exacerbations, have been published [7,8]. One of these was conducted using data from MENSA and MUSCA studies, and also assessed the annual rate of clinically significant exacerbations in patients receiving mepolizumab 100 mg SC or placebo according to the use of maintenance oral corticosteroids [8].

The results of these studies are aligned with the ones we have obtained and revealed that previous OCS maintenance use shows no influence on exacerbation rate reduction with mepolizumab. Nonetheless, the higher eosinophil levels are associated with a better response to mepolizumab in terms of exacerbation rate reduction[9], as reported for other biologicals [10].

The present study did not aim to evaluate the capacity of mepolizumab to reduce or suspend OCS needs; this was previously demonstrated in the SIRIUS study [4]. Even more so, the response to a biologic is based on improvement of more parameters besides exacerbations, which have not been analyzed here. Nonetheless, exacerbations are one of the most relevant criteria when evaluating drug efficacy in severe asthma. The fact that OCS-dependent patients respond as well as non-OCS-dependents to mepolizumab, in terms of exacerbation rate reduction, constitutes a point in favor for mepolizumab, when considering biological options for steroid dependent asthmatics.

Several aspects of this analysis require further discussion. This was a post hoc analysis and the sample size in each analysis group was small. Randomized study with an appropriate sample size to assess the endpoint of interest would be required to get a

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more conclusive results and minimize the chance of false positive and false negative results.

The effect of the OCS maintenance use on blood eosinophil levels is well documented; this post-hoc analysis shows that there might be evidence that in corticosteroid dependent patients, the benefit of mepolizumab in terms of reducing exacerbations seems not to be influenced by previous maintenance treatment with OCS, however due to small sample size results need to be interpreted with caution.

Conflicts of interest

This is a GSK funded post-hoc analysis of studies NCT01000506 & NCT01691521. All listed authors meet the criteria for authorship set forth by the International Committee for Medical Journal Editors.

I Bobolea and Melero C. have no relevant competing interests to disclose. Sánchez-Herrero M.G., Joksaite S. and Bañas D. are GSK employees. De Andrés, A. was an employee of GSK at the time this analysis was conducted.

Previous presentations

This work has been presented as a poster during the ISAF Congress, Madrid, November 2018.

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Table 1. Exacerbation annual rates according to baseline OCS use stratified by baseline blood eosinophil levels.

Baseline OCS maintenance treatment	Baseline blood eosinophil count		150-300/µL	300-500/µL	≥500/µL	All
Yes	n=243(groups1-4) (Placebo/Mepolizumab)		1. 20/56	2. 18/50	3.33/66	4.71/172
	Exacerbation Annual Rate	Placebo	2.57	2.30	3.11	2.84
		Mepolizumab	1.57	1.26	0.99	1.29
		Rate Ratio Mepolizumab/Placebo 95% CI	0.59 (0.31, 1.11)	0.55 (0.29, 1.05)	0.32 (0.20, 0.51)	0.45 (0.33, 0.63)
No	n= 677(groups 5-8) (Placebo/Mepolizumab)		5.66/168	6.58/130	7.83/172	8.207/470
	Exacerbation Annual Rate	Placebo	1.04	1.45	2.25	1.65
		Mepolizumab	0.77	0.99	0.66	0.81
		Rate Ratio Mepolizumab/Placebo 95% CI	0.72 (0.42, 1.22)	0.68 (0.44, 1.05)	0.30 (0.21, 0.42)	0.49 (0.38, 0.63)
All	n= 920 (Placebo/Mepolizumab)		86/224	76/180	116/238	278/642
	Exacerbation Annual Rate	Placebo	1.41	1.64	2.49	1.94
		Mepolizumab	0.95	1.06	0.75	0.92
		Rate Ratio Mepolizumab/Placebo 95% CI	0.67 (0.45, 1.01)	0.64 (0.45, 0.92)	0.30 (0.23, 0.40)	0.48 (0.39, 0.58)