

FUNDING INFORMATION

None.

CONFLICT OF INTEREST

The authors declare that they have no competing interests.

CONSENT FOR PUBLICATION

Written informed consent for the publication of this case report and any accompanying images was obtained from the patients. A copy of the written consent is available for review by the journal's editor.

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SUPPORTING INFORMATION

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RELlight: A two-year REal-Life study of mepolizumab in patients with severe eosinophilic asthma in Greece: Evaluating the multiple components of response

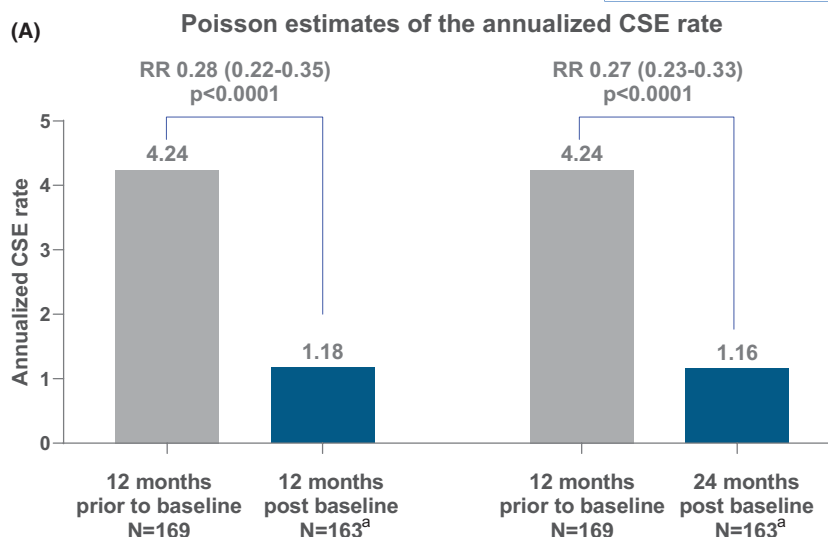
To the Editor,

Limited number of prospective studies exist in terms of the efficacy and safety of mepolizumab in the real-life setting, particularly with 2 years observation period.^{1,2} In our study, we aimed to determine the clinical benefit and safety profile of mepolizumab in patients with severe eosinophilic asthma. Clinical benefits were defined by improvement in different aspects of asthma severity like rate of exacerbations, steroid sparing effect, asthma control, and lung function.

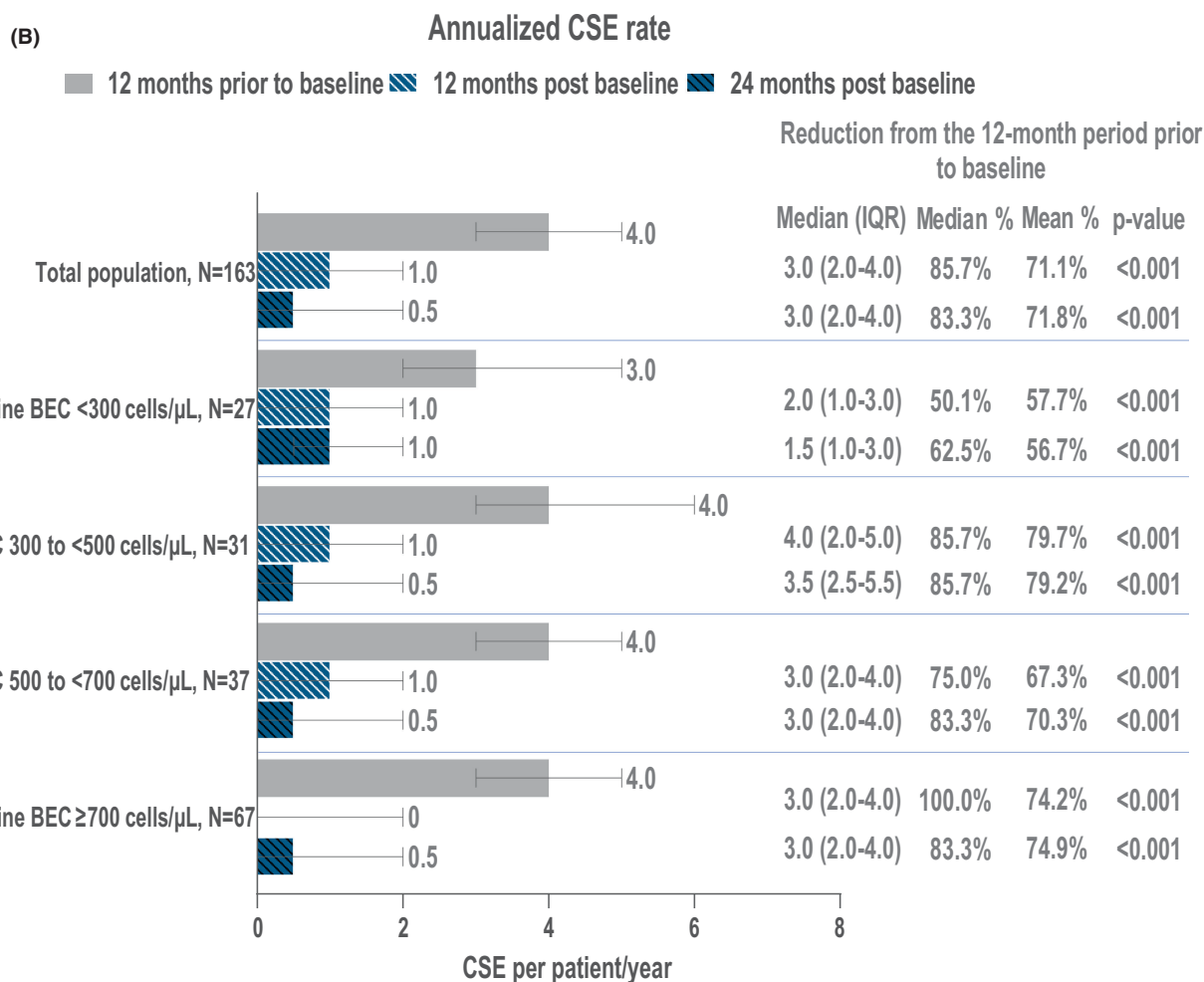
This study was a prospective multicenter, non-interventional observational study. All patients were diagnosed as severe asthmatics based on ERS/ATS criteria.³ Inclusion criteria were the following: age ≥18 years, severe eosinophilic asthma, characterized by an

inadequate symptom control despite a continuous therapy with high doses of Inhaled corticosteroids (ICS) plus long-acting β₂-adrenergic agonists (LABA), peripheral blood eosinophils ≥150 cells/μL in a recent measurement or ≥300 cells/μL in any measurement during the previous year, newly initiated treatment with mepolizumab according to physicians decision, and a history of at least two asthma exacerbations in the previous year despite optimal treatment. The only exclusion criterion was the patients' refusal to participate in the study. As asthma clinically significant exacerbations (CSE) were defined as symptoms deterioration requiring the use of systemic corticosteroids or increase from maintenance dose for at least 3 days and/or emergency visit or hospital admission.

Methodological procedures are provided in the Appendix S1.



^aSix patients discontinued study participation before the 4-month study visit.



169 patients were eligible for the study. Patient demographics are shown in Table S1. In Figure S1, a flow-chart of patient disposition and study visit attendance is provided.

After 1 year of treatment, there was a clinically significant reduction of asthma exacerbations from 4.3 ± 1.9 to 1.2 ± 1.8 , $p < .001$,

(71.1% reduction, $p < .001$) that was maintained after 2 years of treatment, 4.3 ± 1.9 to 1.2 ± 1.6 (71.8% reduction, $p < .001$, Figure 1A). For the patients that completed the 24-month visit ($n = 134$), after 2 years of treatment with mepolizumab, 43 (32.1%) patients were exacerbation-free. Stratifying patients according to baseline blood

FIGURE 1 (A) Annualized CSE rates over the 12-month period prior to baseline and over the 12- and 24-month periods post-baseline estimated using Poisson generalized estimating equation regression model. Annualized rate ratio (RR) along with 95% confidence intervals and p-value of the change is indicated. (B) Annualized CSE rate over the 12-month period prior to baseline and over the 12- and 24-month periods post-baseline in the overall study population and in subpopulations of patients categorized according to their baseline BEC levels. Annualized CSE rates over the 12- and 24-month periods post-baseline show statistically significant ($p < .001$) reduction over that of the 12-month period prior to baseline in the total study population and in all baseline BEC level defined categories. Median (IQR), median and mean % reduction from the 12-month period prior to baseline is displayed for the post-baseline timepoints. The analysis was performed based on data as observed. BEC, blood eosinophil counts; CSE, clinically significant exacerbation; IQR, interquartile range; N, number of patients with available data; RR, rate ratio

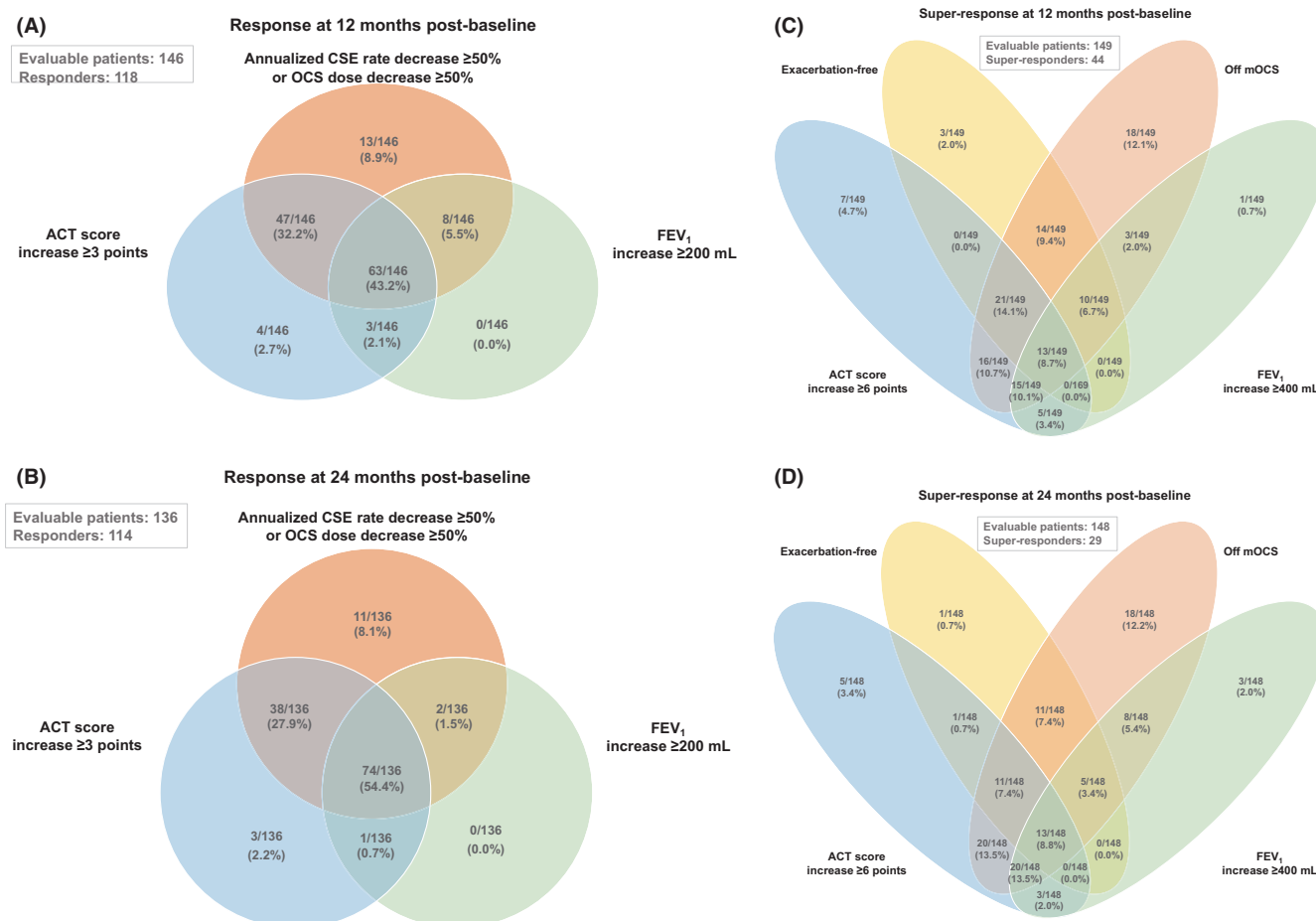


FIGURE 2 Proportions of patients who fulfil each of the response (A and B) and super-response criteria (C and D) at 12 and 24 months post-baseline. Response was defined as achievement of (i) at least 50.0% reduction in annualized CSE rate or in the OCS dose (for OCS-treated patients at baseline) and one of the following: (ii) at least 3-point increase in ACT score, or (iii) at least 200ml increase in FEV₁ volume from baseline. Super-response was defined as (i) achievement of exacerbation-free status and being off mOCS and at least one of the following: (ii) at least 6-point increase in ACT score, or (ii) at least 400ml increase in FEV₁ volume from baseline. Percentages are calculated based on the number of response or super-response-evaluable patients at each of the two timepoints. ACT, asthma control test; CSE, clinically significant exacerbation; FEV₁, forced expiratory volume in one second; IQR, interquartile range; mOCS, maintenance oral corticosteroids; OCS, oral corticosteroids

eosinophils absolute count [BEC] (<300, 300 to <500, 500 to <700 and ≥ 700 cells/ μ L) the annualized CSE 12 and 24 months post-baseline versus the CSE 12 months prior to baseline were significantly lower at all levels but with better improvement in those with BEC > 300 ($p < 0.001$, Figure 1B). Blood eosinophil count, asthma control test, lung function, OCS use, and other asthma medications are provided as an Appendix S1.

Figure 2 depicts/outlines the number and the percentage of responders (Figure 2A, B) and super responders (Figure 2C, D) that achieved a clinically relevant response or super-response in each of the evaluated parameters (ACT, exacerbation reduction, OCS reduction, FEV₁) at 12 and 24 months.

Univariable (Table S2) and multivariable (Table S3) logistic regression analyses were performed to examine the association of

various factors of interest with the achievement of response at 24 months post-baseline. The best-fitted multivariable model included the following factors: gender, presence of GERD at baseline, duration of asthma, FEV1 (percent predicted), number of CSEs in the previous year, and response achievement at 4 months post-baseline. Predictors of response were gender, with males having 84% lower odds of responding to mepolizumab after 24 months of treatment compared with females (OR = 0.16, 95% CI 0.04–0.59, $p = .006$), CSE count in the year prior to baseline, with patients with 3 or less CSEs having 77% lower odds of responding after 24 months than those with >3 CSEs (OR = 0.23, 95% CI 0.07–0.73, $p = .012$), and response attainment as early as 4 months post-baseline, with patients achieving early response having about 5 times higher odds of attaining a response after 24 months of treatment (OR = 5.33, 95% CI 1.69–16.77, $p = .004$). Safety data is provided as Table S4.

Our Venn diagram analysis provides a visual confirmation that the majority of patients can be considered as responders, with a smaller proportion achieving at least one characteristic that would classify them as super responders in one or more of the evaluated parameters. The lower rate of super responders represents our clinical experience that a smaller proportion of patients present an exceptional response, while a higher proportion of patients demonstrate a clinically relevant response to many parameters, and these are still characterized as responders. Representative studies using prospective and/or retrospective data have previously confirmed the higher rate of responders compared with those of super responders.^{4,5} One possible limitation is the fact that only those patients who continue with mepolizumab are analyzed at 24 months, leading to a “selection-bias”, because patients who continue therapy are presumably those who experience greater improvement.

Summarizing our data, in this prospective 2-year follow-up study, we showed that the administration of mepolizumab resulted in lower rates of exacerbations, elimination of OCS intake, better asthma control and improvement of lung function. All the above were driven by the absence of safety issues indicating that mepolizumab is an effective but also safety approach in patients with severe eosinophilic asthma.

CONFLICT OF INTEREST

Konstantinos Glynos is a GlaxoSmithKline employee (Medical Advisor). Evangelia Fouka, Konstantinos Porpodis, Eleni Tzortzaki, Michael Makris, Andriana I. Papaioannou, Konstantinos Katsoulis, Nikoletta Rovina, Petros Bakakos, Paschalis Steiropoulos, Konstantinos Samitas, Konstantinos Kostikas, Stelios Loukides have received payment or honoraria for lectures, presentations, speakers bureaus, manuscript writing or educational events by GSK. The other authors have no relevant conflicts of interest.

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DATA AVAILABILITY STATEMENT

The data that support the findings of this study are available from the corresponding author upon reasonable request.

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SUPPORTING INFORMATION

Additional supporting information may be found in the online version of the article at the publisher's website.

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Metabolomics to identify omalizumab responders among children with severe asthma: A prospective study

To the Editor,

In this study, we aimed to assess the potential value of baseline urinary metabolomic profiles in predicting the response to omalizumab in children with severe asthma. Although most children show a good response to this drug,¹ 10–15% are partial or non-responders.² Identifying the patients most likely to benefit from

omalizumab is crucial to personalise the treatment and optimise cost-effectiveness. So far, clinical or biochemical predictors of response to omalizumab have not been definitively recognised. Metabolomic analysis, using an untargeted approach, has the potential to enable the identification of metabolic features associated with relevant clinical outcomes.³

*See Acknowledgement for all the members of IPSAN.

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