

of rapamycin hyperactivation, although the study results have not yet been reported (<http://www.isrctn.com/ISRCTN92545532>). Given the very favorable safety profile of metformin in pregnancy (5), if found to be effective, this biguanide might be a viable option for the treatment of pregnant patients with LAM. As mentioned by Dr. Yanagisawa, conducting subgroup analyses of previous mechanistic target of rapamycin inhibitor trials in LAM or retrospective case control analyses of patients with LAM already receiving biguanides are reasonable first steps toward the ultimate goal of performing pivotal trials. With respect to the other potential therapeutic options for LAM mentioned, the use of doxycycline in LAM has been the subject of a randomized, double-blind, placebo-controlled clinical trial (6). Although underpowered, this study failed to demonstrate clinical benefit from doxycycline, and routine use of doxycycline in LAM is not recommended (3). In a retrospective review of the NHLBI's intramural LAM cohort, the use of statins did not affect the rate of decline of FEV₁ and was associated with a faster rate of decline of diffusion capacity of carbon monoxide compared with age-matched control patients (7). A subsequent retrospective analysis of the same cohort demonstrated no increase in adverse effects when simvastatin was used in combination with sirolimus (8). A phase 1 clinical trial investigating the safety and efficacy of combined simvastatin and mechanistic target of rapamycin inhibitors in patients with LAM has recently completed enrollment (ClinicalTrials.gov identifier: NCT02061397), and the results should be available soon. However, the safety of statins during pregnancy remains questionable (9), and they may not be a viable option to treat pregnant patients with LAM. Numerous other agents have shown promise as therapeutic options for LAM in preclinical studies, and many are in early-stage clinical trials (10–13). We are hopeful that these studies will lead to an expanded repertoire of drugs for treatment of LAM in the near future. ■

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Rigor Is Needed When Making Comparative Analyses of Biologics in Severe Asthma

To the Editor:

We read with caution the study by Mukherjee and colleagues in which they reported observations from a 24-week single-blind study of 10 prednisone-dependent patients (1). The described study is nonrandomized and retrospectively compares intravenous reslizumab treatment with subcutaneous mepolizumab treatment in a subset of patients from the previously reported COSMOS (A Study to Determine Long-Term Safety of Mepolizumab in Asthmatic Subjects) study (2), described by the authors as phase 1. These elements of study design and population require further clarification because they have implications with regard to the robustness of the conclusions of the paper.

The patients included in the study by Mukherjee and colleagues were from one center of the multicenter, 52-week, open-label

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extension COSMOS study. COSMOS enrolled patients directly from the 24-week, double-blind (mepolizumab vs. placebo), randomized, placebo-controlled, SIRIUS (Mepolizumab Steroid-Sparing Study in Subjects with Severe Refractory Asthma) steroid-sparing study (3). Thirteen patients from SIRIUS (eight receiving mepolizumab and five receiving placebo) entered COSMOS (phase 1) from this center. The demographics and clinical outcomes of this subpopulation were previously reported by Sehmi and colleagues (4) and demonstrated that mepolizumab-treated patients responded with a reduction in blood eosinophils, a trend toward sputum eosinophil reduction, a reduction in maintenance oral corticosteroid (OCS) dose, and an improvement in asthma control questionnaire scores as compared with placebo. In the study described by the authors, this subpopulation was without mepolizumab treatment for at least a 14-month period, during which time they were seen in clinical practice and reestablished on an optimized maintenance OCS dose, after which 10 of the 13 patients enrolled in the interventional phase of this study (phase 2). An understanding of the patients' journey through the various studies is particularly relevant because the patient demographics and premepolizumab baseline data reflect data summarized from a mixed population of mepolizumab- and placebo-treated patients. When comparing the pre- and postmepolizumab data for the primary outcomes of blood and sputum eosinophils, this translates into less room for improvement as compared with before and after reslizumab. From the data presented, approximately half of the premepolizumab population from COSMOS had a sputum count below the 3% threshold at baseline, and 4 of 10 had a blood eosinophil count of <300 cells/ μL , likely representing the mepolizumab-treated patients from SIRIUS. In contrast, the prerestlizumab baseline data were collected after a 12-month period during which all patients were without mepolizumab treatment, after which, and not unexpectedly (5), all patients had a sputum eosinophil count of $>3\%$ and blood eosinophil count of ≥ 300 cells. These baseline differences make it impossible to draw the conclusion that the magnitude of the treatment effect is greater with reslizumab than with mepolizumab.

With respect to other conclusions regarding efficacy, the authors describe criteria to define responders and nonresponders, including a comparison with baseline for the reduction in blood and sputum eosinophils. This is not a convincing comparison, for the reasons described above. In addition, the authors also inappropriately included occurrence of exacerbations as part of the criteria, comparing the exacerbation rates from a 52-week study

with those from a 16-week study in a sample of 10 patients. The safety data should also be presented in the context of the patients' journey through the different studies; for example, although the total duration of mepolizumab treatment exposure was 52–76 weeks, it was compared here with 16 weeks of reslizumab exposure.

The clinical trial program that supported regulatory approval of mepolizumab in 2015 included over 1,000 patients who participated in randomized, controlled trials across multiple countries and centers. This clinical trial program found that mepolizumab, administered intravenously in DREAM (Dose Ranging Efficacy and Safety with Mepolizumab), and in later studies subcutaneously, led to a significant and consistent reduction in exacerbation rates, and identified the blood eosinophil count as an effective biomarker to indicate clinical response (3, 6, 7). In contrast, the sputum data from a subset in DREAM did not identify a reduction in the percentage of sputum eosinophils as a determinant of exacerbation reduction, irrespective of the baseline level ($\geq$ or $<3\%$) (6). A *post hoc* analysis showed a pharmacodynamic effect, i.e., 78%, 90%, and 93% reductions from baseline in the percentage of sputum eosinophils with 75-, 250-, and 750-mg intravenous doses, respectively, compared with a 5% increase with placebo by 4 weeks of treatment, in those who entered DREAM with a baseline of $\geq 3\%$ eosinophils (Table 1). With respect to mepolizumab's clinical effect in the OCS-dependent population, a *post hoc* analysis from DREAM showed a similar clinical response as measured by exacerbation rate reduction in the OCS- and non-OCS-dependent populations (6, 8). When studied prospectively in the OCS-dependent population (SIRIUS; $n = 135$), mepolizumab (100 mg s.c.) led to an OCS dose reduction that was consistent, when adjusted for placebo, with the results from a previous study of higher-dose mepolizumab (750 mg i.v.) conducted by Nair and colleagues (9), and also consistent, when adjusted for placebo, with the 50% OCS reduction seen in the more recent benralizumab ZONDA (Efficacy and Safety Study of Benralizumab to Reduce OCS Use in Patients with Uncontrolled Asthma on High Dose Inhaled Corticosteroid plus LABA and Chronic OCS Therapy) study (10). Additionally, a sputum substudy of SIRIUS subjects ($n = 13$) demonstrated a trend toward a reduction in the percentage of sputum eosinophils in a population who achieved OCS reduction and improvement in asthma control as measured by the asthma control questionnaire (4). Although it is acknowledged that a further understanding of

Table 1. DREAM Sputum Subgroup Eosinophil Reduction with Mepolizumab

	Placebo ($n = 27$)	Mepolizumab 75 mg i.v. ($n = 20$)	Mepolizumab 250 mg i.v. ($n = 24$)	Mepolizumab 750 mg i.v. ($n = 23$)
Baseline				
Sputum eosinophils $\geq 3\%$, n	16	15	20	15
Sputum eosinophils, %*	22.28 (0.980)	23.55 (0.868)	14.58 (0.938)	19.20 (0.838)
Week 4				
Sputum eosinophils $\geq 3\%$, n	12	9	17	7
Sputum eosinophils, %*	18.72 (1.464)	5.19 (2.174)	1.47 (1.794)	0.74 (1.717)
Ratio to baseline*	1.05 (0.818)	0.22 (1.561)	0.10 (1.849)	0.07 (1.654)

Definition of abbreviation: DREAM = Dose Ranging Efficacy and Safety with Mepolizumab.

*Geometric mean (SD) logs; data were log transformed prior to analysis.

the drivers of eosinophil-mediated disease in the OCS-dependent population is required, the clinical data presented to date for mepolizumab have proven the utility of the blood eosinophil count as a biomarker predictive of treatment response in all studies since DREAM, as well as in a more recent meta-analysis (11).

The work by Mukherjee and colleagues provides interesting mechanistic information about the activation and recruitment of airway eosinophils in the prednisone-dependent population, but to use this nonrandomized, retrospective study to make a conclusive statement that one clinical therapy is superior in efficacy or safety to another is both factually incorrect and scientifically misleading. This trial ($n = 10$) should not be overinterpreted when placed alongside extensive randomized controlled trials of anti-IL-5 therapies. In the era of personalized medicine, it is clear that not all medicines work with the same degree of effectiveness in all patients. However, further research, in properly designed studies, should lead to more refined phenotyping and a greater understanding of which patients might respond best to different therapeutic options. ■

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