Original Article

Mepolizumab Reduces Hypereosinophilic Syndrome Flares Irrespective of Blood Eosinophil Count and Interleukin-5

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What is already known about this topic? Mepolizumab is the first biologic therapy to be approved for the treatment of hypereosinophilic syndrome (HES). Previous studies demonstrated that mepolizumab reduced disease flares and improved fatigue severity versus placebo in patients with HES.

What does this article add to our knowledge? Our analysis shows that mepolizumab is associated with reductions in disease flares and fatigue severity irrespective of baseline blood eosinophil count and also showed efficacy in patients with an undetectable serum interleukin-5 level.

How does this study impact current management guidelines? Patients with HES are likely to achieve clinical benefit with mepolizumab treatment, independent of baseline blood eosinophil count; patients should be considered for mepolizumab treatment irrespective of detectable serum interleukin-5 levels.

BACKGROUND: Mepolizumab, an anti-interleukin-5 (IL-5) antibody, reduces disease flares in patients with hypereosinophilic syndrome (HES). Factors predicting treatment response are unknown.

OBJECTIVE: To assess mepolizumab efficacy by baseline blood eosinophil count (BEC) and serum IL-5 level in patients with HES.

METHODS: This *post hoc* analysis used data from the phase III study assessing mepolizumab in patients with HES (NCT02836496). Patients 12 years old or older, with HES for 6 or more months, 2 or more flares in the previous year, and BEC ≥1,000 cells/μL at screening were randomized (1:1) to 4-weekly subcutaneous mepolizumab (300 mg) or placebo, plus baseline HES therapy, for 32 weeks. The proportion of patients

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Abbreviations used
BEC- Blood eosinophil count
BFI- Brief Fatigue Inventory
HES- Hypereosinophilic syndrome
IL- Interleukin
IS- Cytotoxic and/or immunosuppressive therapies
OCS- Oral corticosteroids

experiencing 1 or more flares (wk 32), annualized flare rate, and proportion of patients with change from baseline in Brief Fatigue Inventory (BFI) item 3 (wk 32), were analyzed by baseline BEC (<1500/≥1500 to <2500/≥2500 cells/μL). Flare outcomes were assessed by baseline serum IL-5 (<7.81/≥7.81 pg/mL).

RESULTS: Across baseline BEC subgroups, mepolizumab reduced the proportion of patients experiencing 1 or more flares by 63% to 90% and flare rate by 58% to 84% (treatment-by-eosinophil interaction $P = .76$ and $P = .90$, respectively); patients had improved BFI item 3 score with mepolizumab versus placebo (cells/μL: <1,500: 54% vs 37%; ≥1,500 to <2,500: 47% vs 31%; ≥2,500: 61% vs 0%; treatment-by-eosinophil interaction $P = .42$). Most patients had undetectable baseline serum IL-5 levels; among these, mepolizumab versus placebo reduced the proportion of patients with 1 or more flares (77%) and flare rate (67%).

CONCLUSIONS: Mepolizumab was efficacious in the patients with HES studied, irrespective of baseline BEC. Undetectable IL-5 levels should not preclude mepolizumab treatment. **(J Allergy Clin Immunol Pract 2022;10:2367-74)**

Key words: *Baseline blood eosinophil count; Flare; Fatigue; IL-5; Hypereosinophilic syndrome; Mepolizumab*

INTRODUCTION

Hypereosinophilic syndrome (HES) is a rare and debilitating multisystem disorder characterized by elevated eosinophil counts in the peripheral blood and tissues and eosinophil-mediated organ damage.[1] Sustained elevated eosinophil counts can affect all organ systems, and as such, the clinical presentation of patients with HES is heterogeneous,[1,2] although skin, lung, cardiovascular, and gastrointestinal involvements are the most common manifestations.[1,3] Ultimately, the extent of organ system dysfunction is linked to the severity of clinical manifestations; therefore, the aim of treatment is to prevent, and if possible, reverse organ damage to improve patient outcome.[2,4,5] With the exception of patients with imatinib-sensitive HES variants, current standard of care treatment for HES includes oral corticosteroids (OCS) and cytotoxic and/or immunosuppressant therapies (IS).[2] However, these have variable clinical efficacy and are associated with substantial side effects.[3,6]

Mepolizumab is a humanized monoclonal antibody that binds to and inactivates interleukin-5 (IL-5), thereby blocking the proliferation, activation, and survival of eosinophils.[7] Mepolizumab is approved for the treatment of severe eosinophilic asthma and eosinophilic granulomatosis with polyangiitis in multiple regions worldwide and, recently, has also been approved for use in patients with HES and chronic rhinosinusitis with nasal polyps.[8-10] The approval of mepolizumab for the treatment of HES was based on the findings from the double-blind, phase III 200622 study (NCT02836496).[11] This study and the open-label extension study (NCT03306043) in patients with HES demonstrated that mepolizumab treatment reduced the frequency of disease flares, fatigue severity, OCS use, and blood eosinophil count (BEC), versus placebo, respectively, with no new safety signals identified,[11,12] which was consistent with an earlier preliminary report.[13]

A relationship between mepolizumab efficacy and baseline BEC has been established for eosinophil-driven diseases such as severe eosinophilic asthma.[10,11] However, the impact of baseline BEC or detectable serum IL-5 level on mepolizumab clinical treatment responses in HES is unknown. We therefore hypothesized that relative elevations in baseline BEC or serum IL-5 level may lead to patients with HES deriving greater clinical benefit from mepolizumab treatment than those patients with a lower baseline BEC or lower serum IL-5 level. The objective of this *post hoc* analysis of data from the 200622 study was to assess the impact of baseline BEC and serum IL-5 level on reductions in flares and fatigue observed with mepolizumab treatment.

METHODS

Study design and patients

This was a *post hoc* analysis of data from the 200622 study, which was a randomized, placebo-controlled, double-blind, parallel-group, multicenter, phase III trial (NCT02836496). Full details of this study have been reported previously.[11] Briefly, after screening, patients were randomized (1:1) to receive subcutaneous injections of mepolizumab 300 mg or placebo every 4 weeks for 32 weeks in addition to their existing HES therapy. The trial was conducted in accordance with the ethical principles of the Declaration of Helsinki, the International Conference on Harmonization Good Clinical Practice guidelines, and applicable country-specific regulatory requirements. All patients provided written informed consent.

Full patient eligibility criteria have been reported previously.[11] In brief, patients were 12 years of age or older at screening and had a diagnosis of HES 6 or more months before screening. Patients with the *FIP1L1-PDGFRA* rearrangement were excluded. An HES diagnosis was based on organ system involvement and/or dysfunction that could be directly related to a BEC >1,500 cells/μL on 2 or more occasions, and/or tissue eosinophilia, without a discernible secondary cause. Patients had to have stable HES therapy for 4 weeks or longer before the baseline visit, had 2 or more flares within the past 12 months and a BEC ≥1,000 cells/μL at screening.

Post hoc analysis outcomes

The end points assessed during this *post hoc* analysis were the proportion of patients who experienced 1 or more flares during the 32-week study period, the annualized rate of flares, and the proportions of patients with increases, no change and reductions from baseline in Brief Fatigue Inventory (BFI) item 3 (worst level of fatigue in past 24 h) at week 32 (primary and secondary end points in the 200622 study, respectively).[11] The BFI item 3 was recorded

TABLE I. Patient baseline demographics and characteristics by baseline BEC

		Baseline BEC (cells/μL)		
Demographic/characteristic	**Total (n = 108)**	**<1,500 (n = 56)**	**≥1,500–<2,500 (n = 31)**	**≥2,500 (n = 21)**
Age, y, mean (SD)	46.0 (15.78)	43.2 (16.91)	47.3 (15.68)	51.5 (11.00)
Female, n (%)	57 (53)	29 (52)	17 (55)	11 (52)
BMI, kg/m^2, mean (SD)	26.29 (5.883)	25.39 (4.445)	27.35 (8.074)	27.12 (5.316)
Duration of HES, y, mean (SD)	5.55 (6.691)	5.38 (7.627)	5.71 (4.346)	5.79 (7.144)
Number of historical flares,* mean (SD)	2.7 (1.2)	2.6 (1.1)	2.7 (1.0)	2.9 (1.4)
Most bothersome HES symptoms,† n (%)				
Abdominal pain or bloating	40 (37)	21 (38)	11 (35)	8 (38)
Breathing symptoms	60 (56)	33 (59)	15 (48)	12 (57)
Chills or sweats	15 (14)	7 (13)	5 (16)	3 (14)
Muscle or joint pain	44 (41)	24 (43)	10 (32)	10 (48)
Nasal or sinus symptoms	41 (38)	26 (46)	8 (26)	7 (33)
Skin symptoms	53 (49)	22 (39)	19 (61)	12 (57)
Baseline HES therapy, n (%)				
Any	99 (92)	51 (91)	27 (87)	21 (100)
OCS	78 (72)	41 (73)	21 (68)	16 (76)
≤20 mg/d‡	72 (67)	38 (68)	19 (61)	15 (71)
>20 mg/d‡	6 (6)	3 (5)	2 (6)	1 (5)
IS	23 (21)	11 (20)	7 (23)	5 (24)
Other	41 (38)	22 (39)	12 (39)	7 (33)
Not taking OCS or IS	25 (23)	13 (23)	9 (29)	3 (14)
OCS‡ daily dose, mg, mean (SD)	8.0 (9.17)	7.2 (8.64)	8.6 (10.48)	9.4 (8.69)
BFI score, mean (SD)	4.57 (2.614)	4.64 (2.662)	4.96 (2.575)	3.78 (2.497)
BEC, geometric mean (SD log) [range]	1,400 (0.832) [30–18,350]	800 (0.677) [30–1,460]	1,900 (0.143) [1,510–2,460]	3,980 (0.508) [2,520–18,350]

BFI, Brief Fatigue Inventory; *BMI*, body mass index; *HES*, hypereosinophilic syndrome; geo, geometric; *OCS*, oral corticosteroid; *SD*, standard deviation.
*In the 12 mo prior to screening.
†As reported by patients; at baseline/randomization, patients reported up to 3 HES-related symptoms that they considered most bothersome.
‡Prednisone or equivalent.

using an eDiary (BFI range 0–10; higher score indicates worse fatigue). The minimal clinically important difference in BFI item 3 for patients with HES was not determined. In the 200622 study, flares were defined as (1) an HES-related clinical manifestation (based on a physician-documented change in clinical signs or symptoms) that required either an increased dose of maintenance OCS of 10 or more mg prednisone equivalent/d for 5 days or an increase in/addition of any IS HES therapy or (2) receipt of 2 or more courses of blinded OCS during the treatment period.[11] This *post hoc* analysis included flares meeting either definition.

Baseline serum total IL-5 categories (undetectable [<7.81] or ≥7.81 pg/mL) were analyzed by baseline OCS use (yes/no) *post hoc*. All end points were analyzed by prespecified baseline (ie, the randomization visit) BEC categories (<900, ≥900 to <1,500, ≥1,500 to <2,200, ≥2,200 cells/μL). For this *post hoc* analysis, baseline BEC was categorized into <1,500, ≥1,500 –<2,500 and ≥2,500 cells/μL, on the basis of their clinical relevance and to improve the statistical power for each subgroup. Baseline BECs were measured at the randomization visit, up to 4 weeks after screening (note: patients received stable HES therapy for ≥4 wks prior to baseline and throughout the 32-wk treatment period). Flare end points were also assessed according to serum IL-5 at baseline, based on the limit of detection for serum IL-5 (undetectable [<7.81] or ≥7.81 pg/mL). At baseline, week 32, and in the event of a flare, serum samples were collected for measurement of IL-5 levels by enzyme-linked immunosorbent assay; free and total IL-5 were measured with a detection range of 3.91 to 500 pg/mL and 7.81 to 500 pg/mL, respectively.

Statistical analysis

Full details of the statistical analysis for the 200622 study have been published previously.[11] Briefly, the proportion of patients with a flare was analyzed using a logistic regression analysis adjusted for treatment and baseline OCS dose. Patients who withdrew prematurely from the study were included in the analysis as having a flare. The annualized rate of flares was analyzed using a negative binomial regression model with covariates of baseline OCS dose, region, baseline BEC, and observed time (as an offset variable). Change from baseline in fatigue severity at week 32 was summarized and the median change in BFI item 3 was presented. Patients with missing data were included in this analysis with the largest (ie, worst) value observed for any patient. Change from baseline in fatigue severity at week 32 (BFI item 3) was analyzed using mixed model repeated measures with covariates of baseline OCS dose, baseline BEC, region, treatment, and visit, plus interaction terms for visit-by-baseline, visit-by-treatment group, and visit-by-baseline BEC. All analyses were performed using SAS software, version 9.4 (SAS Institute, Cary, NC).

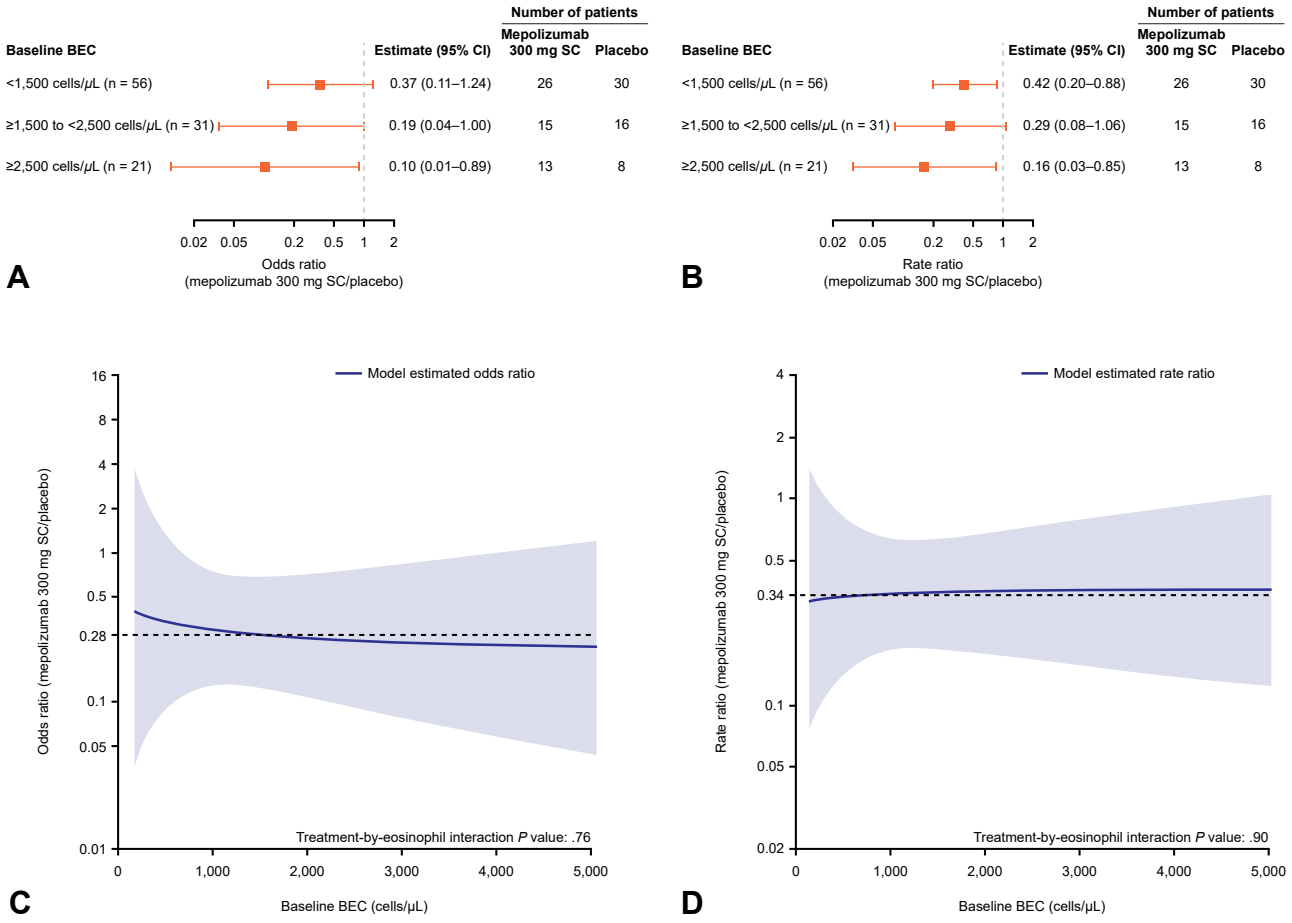

FIGURE 1. (**A** and **C**) Proportion of patients experiencing flares and (**B** and **D**) annualized rate of flares during the 32-wk treatment period by baseline BEC. (**C** and **D**) The shaded area represents 95% CIs; the reference line represents the result for the overall population. *CI*, confidence interval; *SC,* Subcutaneous.

RESULTS

Patient baseline demographics and clinical characteristics

Baseline demographics and clinical characteristics of the 108 patients who participated in the 200622 study have been previously reported.[11] Within the total population, 56 patients had a BEC <1,500 cells/μL, 31 had ≥1,500 to <2,500 cells/μL, and 21 had ≥2,500 cells/μL at baseline; patient demographics and clinical characteristics according to baseline BEC subgroups are shown in Table I. Patients with a baseline BEC ≥1,500 cells/μL (ie, ≥1500 to <2500 and ≥2500 cells/μL) were numerically older, had a slightly longer duration of HES, a higher number of historical flares, and were receiving a higher daily OCS dose than patients with a BEC <1,500 cells/μL. Furthermore, a greater proportion of patients with a baseline BEC of ≥1,500 cells/μL (ie, ≥1,500 to <2500 and ≥2500 cells/μL) reported skin symptoms as a most bothersome symptom, and fewer patients reported nasal or sinus symptoms than patients with a BEC <1500 cells/μL.

Impact of mepolizumab by baseline BEC

The odds of a patient experiencing 1 or more flares was reduced by at least 63% with mepolizumab versus placebo, across all baseline BEC subgroups; patients with ≥2,500 cells/μL experienced the greatest reduction (Figure 1, *A*). However, modeling analyses indicated no significant interaction between baseline BEC and mepolizumab efficacy ($P = .76$; Figure 1, *C*). Likewise, mepolizumab treatment was also associated with at least a 58% reduction in the annualized rate of flares versus placebo, across all baseline BEC subgroups. Patients with ≥2,500 cells/μL experienced the greatest reduction in the annualized rate of flares with mepolizumab versus placebo (Figure 1, *B*), although the modeling analysis indicated no significant interaction between BEC count and mepolizumab treatment ($P = .897$; Figure 1, *D*).

In all baseline BEC subgroups, a higher proportion of patients treated with mepolizumab versus placebo demonstrated an improvement from baseline in fatigue severity (BFI item 3) score at week 32 (Figure 2, *A*–*C*). However, the modeling analysis indicated no significant interaction between baseline BEC and mepolizumab treatment ($P = .423$; Figure 2, *D*). Of note, in patients receiving placebo, a greater proportion with a baseline BEC from ≥1,500 to <2,500 cells/μL (62%) or ≥2,500 cells/μL (63%) had a worsening of BFI item 3 score at week 32 compared with placebo-treated patients who had a baseline BEC <1,500 cells/μL (29%; Figure 2, *A*–*C*).

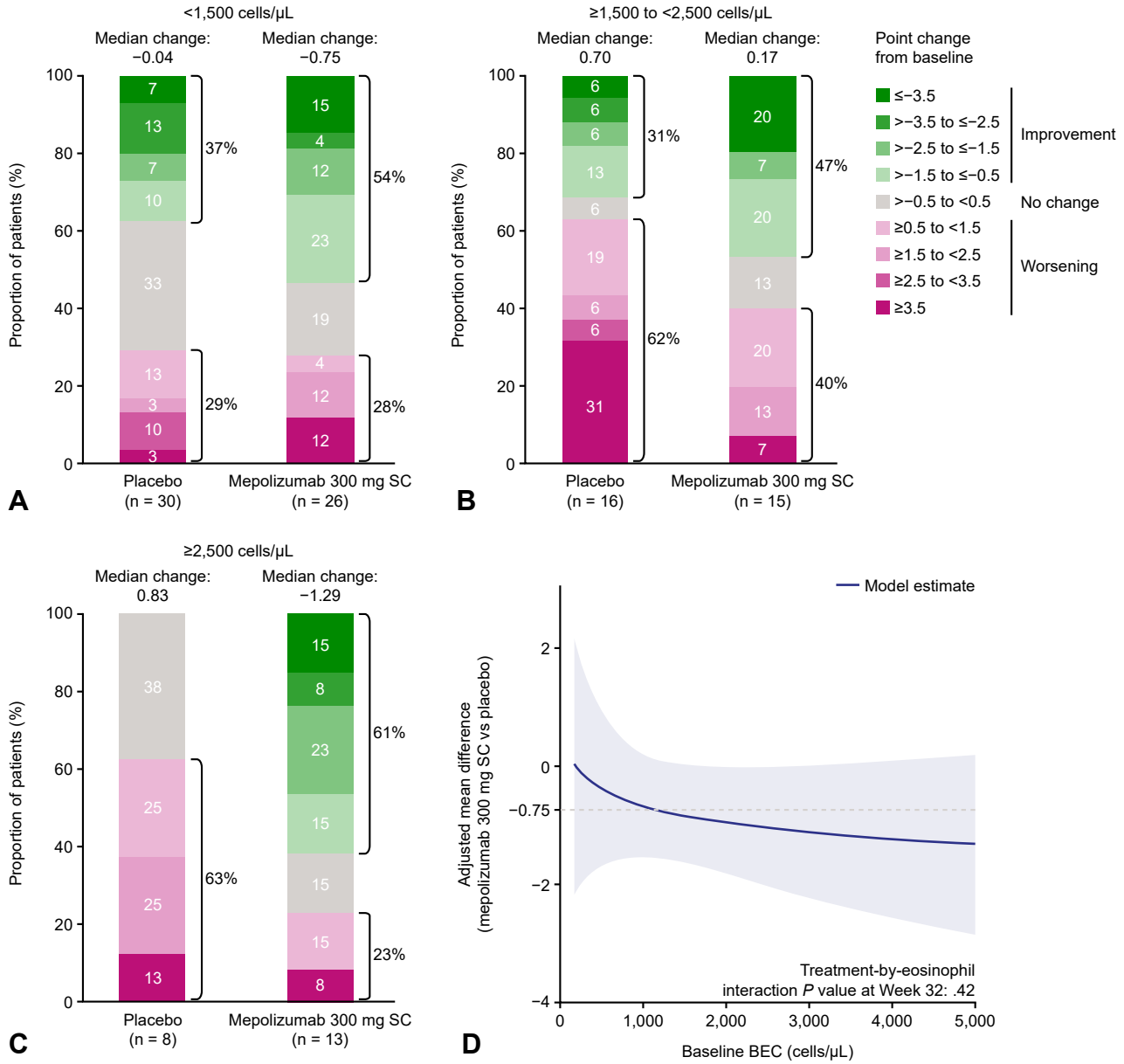

FIGURE 2. (**A**–**C**) Change from baseline in BFI item 3 score (worst level of fatigue in past 24 hours) at wk 32 by baseline BEC and treatment arm. (**D**) The shaded area represents 95% CIs; the reference line represents the result for the overall population. *SC*, Subcutaneous.

Impact of mepolizumab by baseline serum IL-5 level

The majority of patients (79.6%; n = 86) had an undetectable baseline serum IL-5 level (≤7.81 pg/mL; Figure E1; available in this article's Online Repository at www.jaci-inpractice.org), irrespective of whether they were treated with OCS at baseline (with OCS use: 77%; no OCS use: 87%; Table E1; available in this article's Online Repository at www.jaci-inpractice.org). The BEC in patients receiving placebo was similar across serum IL-5 level thresholds and for the duration of the study (Figure 3). The baseline BEC for patients with an undetectable serum IL-5 level (<7.81 pg/mL) was similar between mepolizumab and placebo groups (1,360 cells/μL; Figure 3, *A*), whereas the baseline BEC in patients with a detectable baseline serum IL-5 level (≥7.81 pg/mL) was higher in those receiving mepolizumab than placebo (2,190 cells/μL vs 1,330 cells/μL; Figure 3, *B*). In patients receiving mepolizumab, the BEC decreased after baseline and remained low for the duration of the study (≤250 cells/μL), irrespective of baseline serum IL-5 threshold (Figure 3).

For patients with an undetectable baseline serum IL-5 level (<7.81 pg/mL), mepolizumab treatment was associated with a 77% reduction in the proportion of patients experiencing 1 or more flares versus placebo; no treatment effect was observed in patients with a detectable serum IL-5 level (≥7.81 pg/mL; Figure 4); however, the number of patients in this subgroup was small (n = 22). Mepolizumab treatment was also associated with a 67% reduction in the annualized rate of flares in patients with an undetectable IL-5 level versus placebo; in patients with a detectable IL-5 level, a 54% numerical

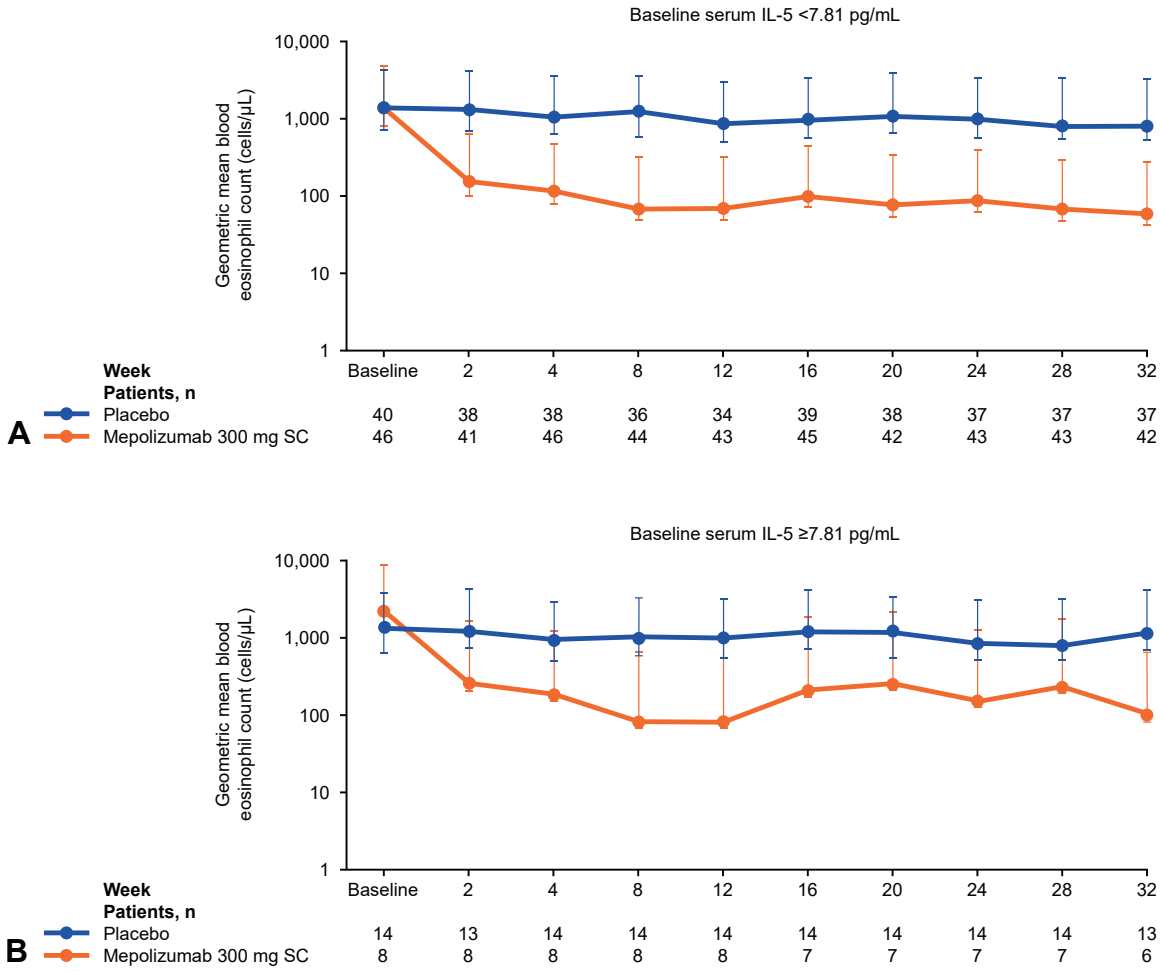

FIGURE 3. BEC over time stratified by baseline serum IL-5 level (**A**) <7.81 pg/mL and (**B**) ≥7.81 pg/mL. Error bars represent SD logs. Data were log transformed prior to analysis; where a result of 0 was recorded, this was replaced with 0.005 prior to log transformation. *SC*, Subcutaneous.

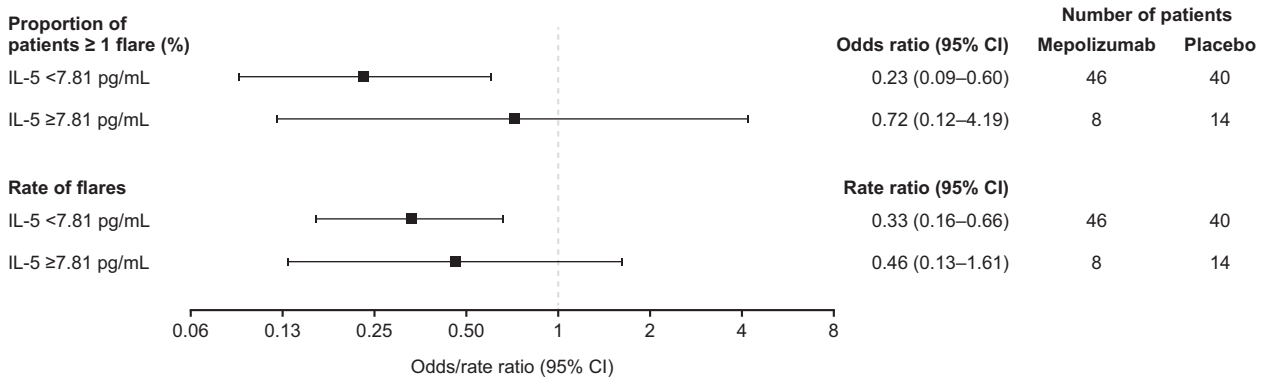

FIGURE 4. Proportion of patients experiencing a flare and annualized rate of flares during the 32-wk treatment period by baseline serum IL-5 level. Odds/rate ratio <1 indicates a lower proportion of patients with ≥1 flare or a lower flare rate with mepolizumab versus placebo. *CI*, confidence interval.

reduction in the annualized rate of flares was observed with mepolizumab versus placebo, although the confidence intervals were large (Figure 4).

DISCUSSION

BEC are a well-established biomarker for predicting the response to mepolizumab treatment in patients with severe

eosinophilic asthma.[14,15] However, for rare and heterogeneous diseases such as HES, determining the impact of a particular biomarker on the likelihood of a treatment response is more challenging, in part owing to the lower prevalence, heterogeneity in the underlying pathogenic mechanisms, and variable clinical presentation of the disease.[16] The current analysis demonstrated that mepolizumab reduced the proportion of patients experiencing 1 or more flares during the 32-week treatment period, reduced the annualized rate of flares, and reduced fatigue severity versus placebo, irrespective of baseline BEC and in patients with undetectable serum IL-5 at baseline. Furthermore, our modeling analysis did not suggest a treatment effect with increasing BEC, either for the proportion of patients with at least one flare, the annualized flare rate, or fatigue severity, although it is worth noting that the small sample size may not have been powered to drive statistical results. These data highlight the consistent clinical benefit with mepolizumab in patients with HES across a range of baseline BECs and for patients with undetectable serum IL-5.

While evidence of elevated blood and/or tissue eosinophil counts is critical for a diagnosis of HES, the available evidence is limited to support a sole role for eosinophil counts in determining severity of disease.[17,18] Our data showed that patients with a baseline BEC $\geq$1,500 cells/μL were typically older, had a slightly longer duration of HES, had a higher number of historical flares, and were receiving a higher daily OCS dose than patients with a BEC <1,500 cells/μL, suggestive of more severe disease in patients with a higher BEC. As such, the finding that mepolizumab was associated with improvements in the number and rate of flares and fatigue across all BEC subgroups indicates the benefit of mepolizumab, including in patients with more severe disease. Notably, these analyses were also performed in baseline BEC subgroups with thresholds (based on quartiles) that were prespecified in the original study analysis plan (Table E2; available in this article's Online Repository at www.jaci-inpractice.org). The outcomes in these subgroups were in line with the findings from this *post hoc* analysis, indicating mepolizumab was efficacious across all baseline BEC groups tested. In keeping with these findings, the modeling analyses did not support a treatment effect with increasing baseline BEC, which further supports the consistent effect of mepolizumab across the HES patient population, irrespective of BEC.

Given mepolizumab's mechanism of action, we also assessed the impact of baseline serum IL-5 level on the number and rate of flares with mepolizumab treatment. These results did not indicate a change in treatment effect for mepolizumab with an increasing baseline serum IL-5 level for any of the outcomes measured in the small number of patients with detectable IL-5. However, we did demonstrate that mepolizumab was efficacious in patients with an undetectable baseline serum IL-5 level. A lack of association between biologic treatment responses and the associated target cytokine has been reported in other eosinophilic diseases as well as in other diseases with an underlying inflammatory pathophysiology.[19,20] Our results are also consistent with a previous report assessing mepolizumab efficacy in patients with HES, in which most patients had an undetectable serum IL-5 level at baseline, although clinical response parameters were not assessed.[13] In contrast, a retrospective observational study of patients treated with intravenous mepolizumab (750 mg), demonstrated that clinical responses correlated with pretreatment serum IL-5 levels.[21] It is important to note that the inclusion criteria for that study were more stringent than those employed in our study because patients with life-threatening HES with at least 3 prior failed conventional HES therapies were eligible for inclusion.[21] Nonetheless, our results are of significant clinical relevance because they suggest that a detectable serum IL-5 level is not a prerequisite for treatment with mepolizumab and that patients with HES are likely to experience clinical benefit with mepolizumab even if they have undetectable levels of serum IL-5.

The limitations of the parent study have been reported previously.[11] For the current analysis, the *post hoc* nature is a key limitation, and in particular, the small patient numbers included in each baseline BEC subgroup and in the detectable baseline serum IL-5 level subgroup. Power calculations for this study have been reported previously,[11] estimating a sample size of 120 patients was required to detect an absolute reduction of 38% in the proportion of patients experiencing a flare during the study. As we reported data from 56, 31, and 21 patients with a baseline BEC <1,500 cells/μL, $\geq$1,500 to <2,500 cells/μL, and $\geq$2,500 cells/μL, respectively, the significance testing for this analysis was underpowered. In addition, most patients had an undetectable baseline serum IL-5 level, limiting the interpretation of the impact of baseline serum IL-5 level on mepolizumab efficacy. It is also worth noting that 72% of patients in the study were using OCS in the 12 months prior to the study and 21% were using cytotoxic/immunosupressive in this period. OCS use has been reported to reduce BECs[22]; therefore, the decision to stratify our analyses by baseline BEC may have been confounded by background OCS use. Furthermore, because corticosteroids can repress the transcription of numerous cytokines, including IL-5,[23,24] prior treatment may have impacted the IL-5 levels seen at baseline, although the *post hoc* analyses did not support this (Table E1). While our findings are valid for this patient population, further investigation into the utility of baseline BEC in predicting treatment responses to mepolizumab in the heterogeneous patient population attending clinical practice is required. Nonetheless, this analysis provides clinically relevant information on the effect of mepolizumab in patients with HES across a range of baseline BECs and in patients with an undetectable baseline serum IL-5 level.

In conclusion, this analysis indicates that patients with HES are likely to achieve clinically important reductions in disease flares and improvements in fatigue with mepolizumab treatment, irrespective of baseline BEC. Our findings suggest that baseline BEC does not significantly influence treatment outcomes with mepolizumab and mepolizumab is also of benefit to patients with an undetectable serum IL-5 level at treatment initiation.

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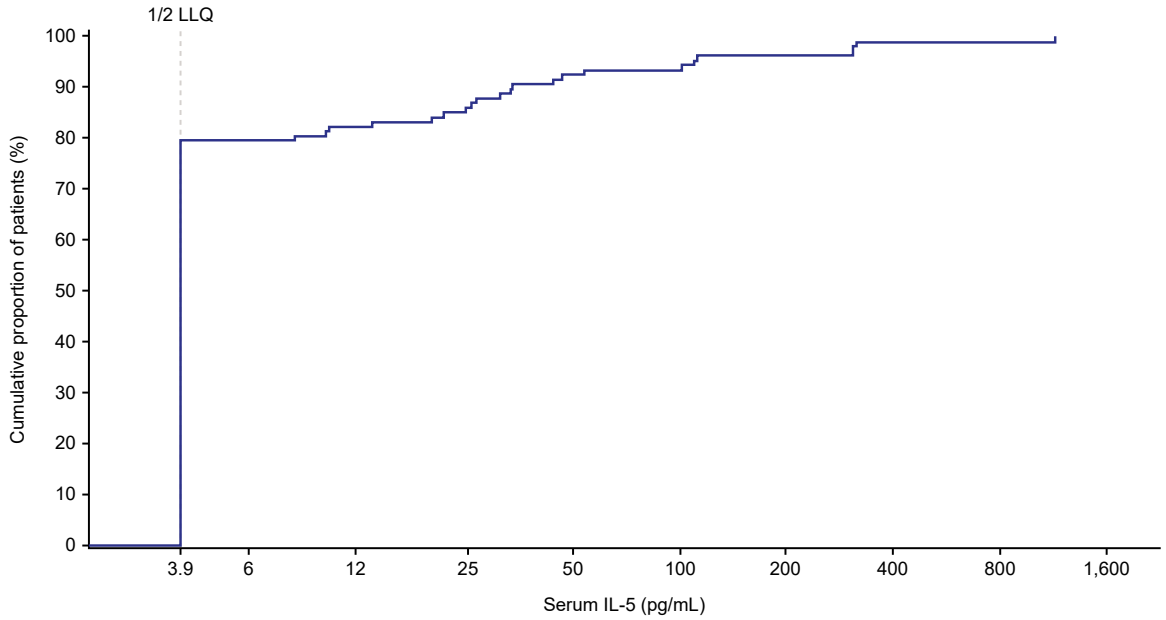

FIGURE E1. Cumulative distribution plot of proportion of patients by baseline serum interleukin-5 (IL-5). Values below the lower limit of quantification (LLQ) were computed using LLQ/2. LLQ value = 7.81 pg/mL.

TABLE E1. *Post hoc* baseline OCS use by baseline serum total IL-5 category analysis

	Baseline serum total IL-5 category (pg/mL)	
Outcome	**<7.81 (n = 86)**	**≥7.81 (n = 22)**
Baseline OCS use, n (%)		
Yes	60 (70)	18 (82)
No	26 (30)	4 (18)

IL, Interleukin; *OCS,* oral corticosteroids.

TABLE E2. Prespecified baseline BEC subgroup analysis

	Baseline BEC category (cells/μL)			
Outcome	**<900 (n = 26)**	**≥900 to <1,500 (n = 30)**	**≥1,500 to <2,200 (n = 25)**	**≥2,200 (n = 27)**
Patients with ≥ 1 flare or who withdrew from the study by wk 32				
Odds ratio (95% CI)*	0.11 (0.01−1.01)	0.89 (0.18−4.42)	0.13 (0.02−0.91)	0.16 (0.03−0.98)
Rate of flares by wk 32				
Rate ratio (95% CI)	0.43 (0.17−1.12)	0.48 (0.13−1.80)	0.22 (0.05−1.02)	0.24 (0.06−0.95)

CI, confidence interval; *HES,* hypereosinophilic syndrome; *OCS,* oral corticosteroids.
*Odds ratio was calculated using a logistic regression analysis adjusted for baseline OCS dose and region. Rate ratios were calculated using a negative binomial regression adjusted for baseline OCS dose. Odds/rate ratio 1 indicates lower rate of flares with mepolizumab compared with placebo.