

Original Article

Safety of Reslizumab in Uncontrolled Asthma with Eosinophilia: A Pooled Analysis from 6 Trials

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What is already known about this topic? The monoclonal IL-5 antibody reslizumab has shown good efficacy and tolerability in patients with severe asthma with eosinophilia in individual placebo-controlled trials lasting up to 52 weeks and in a 2-year open-label study.

What does this article add to our knowledge? This analysis of pooled data in more than 1000 reslizumab-treated patients from placebo-controlled trials and an open-label extension includes data over a longer total duration than previously available. This allows assessment of rare events and demonstrates the good tolerability of reslizumab treatment for a duration of more than 12 months with no evidence of safety issues.

How does this study impact current management guidelines? These data strengthen the evidence base for the good safety and tolerability profile of long-term treatment with intravenous reslizumab 3.0 mg/kg by characterizing rare safety events as well as available long-term data.

BACKGROUND: Intravenous reslizumab, a monoclonal IL-5 antibody, is approved for treating severe asthma with eosinophilia. Limited structured information is available on the safety of reslizumab in larger populations.

OBJECTIVE: To investigate the safety profile of intravenous reslizumab 3.0 mg/kg by analyzing data from 6 asthma clinical trials: 5 placebo-controlled (duration ≤52 weeks) and 1 open-label extension (up to 2 years of treatment).

METHODS: Patients were aged 12 to 75 years with inadequately controlled asthma with eosinophilia. In the placebo-controlled trials, 730 patients received placebo and 1028 received reslizumab 3.0 mg/kg.

RESULTS: Adverse events (AEs) and serious AEs occurred in higher percentages of patients in the placebo group (81% and 9%) than in the reslizumab group (67% and 6%). Asthma, nasopharyngitis, and upper respiratory tract infection were the

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This study was sponsored by Teva Branded Pharmaceutical Products R&D, Inc.

Conflicts of interest: J. C. Virchow has lectured for and received honoraria from Allergopharma, ALK, Asche Chiesi, AstraZeneca, Avontec, Bayer, Bencard, Bionorica, Boehringer Ingelheim, Cipla, Essex/Schering-Plough, GlaxoSmithKline (GSK), Janssen-Cilag, Laboratorios Leti, Meda Pharmaceuticals, Merck/MSD, Mundipharma, Novartis, Nycomed/ALTANA, Pfizer, Regeneron, Revotar Biopharmaceuticals, Sandoz/Hexal, Sanofi, Stallergenes, Takeda, Teva, UCB/Schwarz Pharma, Zydus Cadila, and possibly others; has participated in advisory boards for Asche Chiesi, Avontec, Boehringer Ingelheim, Essex/Schering-Plough, GSK, Janssen-Cilag, MSD, Mundipharma, Novartis, the Paul Ehrlich-Institute, Revotar Biopharmaceuticals, Sandoz/Hexal, Sanofi, Takeda, Teva, UCB/Schwarz Pharma, and possibly others; and has received grants from the Deutsche Forschungsgemeinschaft, Land Mecklenburg-Vorpommern, GSK, and MSD. R. Katial has received fees as a consultant from Teva, AstraZeneca, and Meda, and speaker fees from Meda. G. G. Brusselle has, within the last 5 years,

received honoraria for lectures from AstraZeneca, Boehringer Ingelheim, Chiesi, GSK, Novartis, Pfizer, Teva, UCB, and Zambon; and is a member of advisory boards for AstraZeneca, Boehringer Ingelheim, GSK, Novartis, Sanofi/Regeneron, and Teva. Y. Shalit and M. Garin are employees of Teva Pharmaceuticals. M. McDonald was an employee of Teva Pharmaceuticals at the time the analysis was conducted. M. Castro has received consultancy and speaker fees from Boston Scientific and Genentech; has received consultancy fees from Holaira and Aviragen; has received research support and consultancy and speaker fees from Teva Pharmaceuticals; has received research support from and is on the Data Safety Monitoring Committee for GSK; has received research support and consultancy fees from sanofi-aventis; has received research support and speaker fees from Boehringer Ingelheim and AstraZeneca; has received research support from Amgen, Gilead, Invivo, MedImmune, and Vectura; and receives royalties from Elsevier.

Received for publication December 14, 2018; revised July 30, 2019; accepted for publication July 31, 2019.

Available online ■■

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2213-2198

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<https://doi.org/10.1016/j.jaip.2019.07.038>

Abbreviations used

ADA- Antidrug antibody

AE- Adverse event

CPK- Creatine phosphokinase

ECG- Electrocardiogram

RCT- Randomized controlled trial

RR- Risk ratio

SAE- Serious adverse event

most common AEs with placebo and reslizumab. Three cases of anaphylaxis, related to reslizumab, were successfully managed with standard therapies. No significant difference in the incidence of malignancies was seen when compared with placebo or the general population. Among 756 patients with more than 12 months of reslizumab exposure, the AE rate was lower than in the placebo-controlled trials (367.3 vs 433.9 events/100 patient-years). The incidence of AEs in patients on treatment for more than 12 months was no higher than in patients with shorter treatment durations. CONCLUSIONS: This analysis confirms that treatment with intravenous reslizumab for more than 12 months is well tolerated in patients with asthma, with no evidence of rare safety events that were not detected in individual trials. © 2019 Published by Elsevier Inc. on behalf of the American Academy of Allergy, Asthma & Immunology (J Allergy Clin Immunol Pract 2019;■:■-■)

Key words: Asthma; Eosinophilia; Reslizumab; Pooled analysis; Safety; Tolerability

INTRODUCTION

Inhibition of IL-5 activity benefits patients with inadequately controlled asthma with eosinophilia (eosinophilic asthma).¹⁻³ Reslizumab, an IgG₄ kappa humanized mAb, targets IL-5, thereby disrupting maturation, activation, and survival of eosinophils.^{4,5} Reslizumab is approved in several countries as “add-on” maintenance therapy for patients with severe asthma aged 18 years or older with an eosinophilic phenotype/eosinophilia.⁶⁻⁸

The efficacy of reslizumab has been reported in several studies including phase 3, randomized controlled trial (RCTs).⁹⁻¹³ Compared with placebo, reslizumab reduces asthma exacerbations, and improves lung function (FEV₁), asthma control (Asthma Control Questionnaire scores), and quality of life (Asthma Quality of Life Questionnaire scores). Reslizumab was well tolerated, with a safety profile similar to that of placebo.^{9-11,13,14}

The current analysis’ objective was to characterize the overall safety profile of reslizumab in patients aged 12 to 75 years with inadequately controlled, moderate to severe asthma with eosinophilia. Analysis of pooled data from 6 clinical trials enabled assessment for rare safety events of interest that might not be apparent in individual trials.

METHODS

Data were obtained from 6 clinical trials (Figure 1). All studies were phase 3 except study 1 (NCT00587288), which was phase 2.

Study 1 was a 15-week, randomized, double-blind, placebo-controlled study of reslizumab 3.0 mg/kg as treatment for poorly

controlled asthma in patients (aged 18-75 years) with airway inflammation and elevated sputum eosinophils ($\geq 3\%$).¹⁴

Study 2 (NCT01270464) was a 16-week, randomized, double-blind, placebo-controlled, parallel-group study to evaluate reslizumab 0.3 or 3.0 mg/kg as treatment for patients (aged 12-75 years) with asthma with elevated blood eosinophils (≥ 400 cells/ μ L).⁹

Studies 3 and 4 (NCT01287039 and NCT01285323) were 52-week, double-blind, placebo-controlled, parallel-group studies with identical methodology, to evaluate reslizumab 3.0 mg/kg in the reduction of clinical asthma exacerbations in patients (aged 12-75 years) with asthma with elevated blood eosinophils (≥ 400 cells/ μ L).¹⁰

Study 5 (NCT01508936) was a 16-week, randomized, double-blind, placebo-controlled study to evaluate reslizumab 3.0 mg/kg treatment in patients (aged 18-65 years) with asthma regardless of baseline eosinophil count.¹¹

Finally, study 6 (NCT01290887) was an open-label extension study of long-term treatment (up to 2 years) with reslizumab 3.0 mg/kg for asthma with elevated blood eosinophils.¹³ Patients previously taking placebo in one of the parent studies were switched to active therapy. This study was conducted in patients who had completed study 2, 3, or 4 (recipients of either reslizumab or placebo).

Maintenance oral corticosteroid treatment (prednisone ≤ 10 mg/d or equivalent, representing continuation of patients’ usual asthma treatment) was permitted in studies 3, 4, and 6, but was an exclusion criterion in studies 1, 2, and 5. Inclusion criteria are presented in Table E1 in this article’s Online Repository at www.jaci-inpractice.org. Patients with a history of malignancies were eligible for inclusion in all studies.

Integrated safety-analysis approach

An integrated summary of safety is presented for all patients with asthma who received 1 or more doses of the study drug in placebo-controlled studies with duration of up to 52 weeks (studies 1-5). In addition, the safety of 12-month cumulative exposure to reslizumab was analyzed using data from patients participating in a placebo-controlled trial followed by extension study 6 (Figure 1).

Patients’ demographic and baseline characteristics, study drug exposure, adverse events (AEs), serious adverse events (SAEs), clinical laboratory tests, electrocardiogram (ECG) findings, concomitant medications, and immunogenicity results were analyzed. AEs and SAEs were described using the Medical Dictionary for Regulatory Activities (version 14.0; International Conference on Harmonization, Geneva, Switzerland) terminology.¹⁵ In addition, AEs were analyzed by severity (mild, moderate, or severe), as assessed by the investigator (no limitation of usual activities; some limitation of usual activities; or severe inability to carry out usual activities, respectively). ECG was undertaken only at screening in study 1 and therefore this study was not included in the integrated ECG analysis. Clinical laboratory data from study 1 were excluded because normal ranges and clinical significance criteria were different from those in the other studies; specifically, as the only phase 2 study included in the analysis, study 1 was performed earlier in time. As such, the laboratory criteria used in study 1 differed from those used in the other studies and so the data could not be pooled with those from the other studies. Furthermore, a different method of immunogenicity testing was used in study 1 and the antidrug antibody (ADA) data from this study were not included in the analysis. The arm of study 2 in which patients received reslizumab at 0.3 mg/kg was also not included.

AEs of special interest were systemic hypersensitivity reactions, malignancies, and infections. Observed malignancy rates were

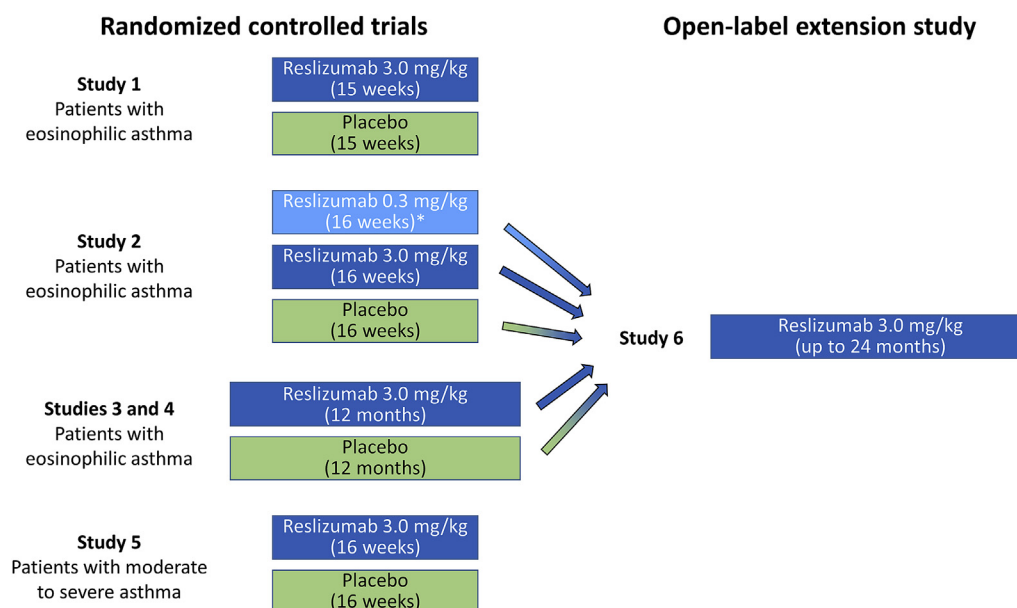


FIGURE 1. Overview of studies included in the safety analysis. *Patients in the reslizumab 0.3 mg/kg arm of study 2 were excluded from the present analysis.

compared with those in the general population via the Surveillance, Epidemiology and End Results database, which includes data from approximately 28% of the US population. An indirect standardization method (standardized incidence ratio) was used for comparison. ADA levels and the potential impact of immunogenicity on the safety profile with respect to asthma-related AEs were also assessed.

Data from the treatment groups were compared by risk ratio (RR), with a null hypothesis that $RR = 1$ (treatment groups are the same). If 1 was not contained within the 95% CI of the RR, then the treatment groups were considered statistically significantly different.

RESULTS: INTEGRATED SUMMARY OF SAFETY

Patient flow and baseline information

A total of 1758 patients were analyzed; 730 received placebo and 1028 reslizumab 3.0 mg/kg. In the placebo-controlled studies, 86.3% of patients overall (placebo, 85.5%; reslizumab, 87.0%) completed treatment. AEs and withdrawal of consent were the most common reasons for withdrawal, with similar incidences in the 2 treatment groups (Figure 2). In total, 963 patients (placebo, 480; reslizumab, 483) continued open-label treatment in study 6 (82.8% of eligible patients from feeder studies 2-4).

Baseline demographic and other characteristics were similar in patients receiving placebo and those receiving reslizumab in the RCTs (Table I). Most (62%) were women; mean ages were 46.4 (placebo) and 45.5 (reslizumab) years.

The proportions of patients at baseline with asthma exacerbations in the preceding 12 months (68% vs 78%) and taking oral corticosteroids (5% vs 8%) were lower among recipients of reslizumab compared with recipients of placebo. Mean blood eosinophil count at baseline was also lower in patients receiving reslizumab than in those receiving placebo (498 vs 586 cells/ μ L; RR, 0.60; 95% CI, 0.56-0.64). These differences are likely to be due to the 3:1 treatment:placebo randomization in study 5; in that study, baseline oral corticosteroid use was an exclusion

criterion and there was no inclusion requirement for historical exacerbations or baseline eosinophil count.

Exposure

Mean duration of treatment in the placebo-controlled studies was 259 ± 131 days and 218 ± 129 days in the placebo and reslizumab groups, respectively. These results translated to 517 and 612 patient-years of exposure, respectively. Among patients with more than 12 months of exposure to reslizumab ($n = 756$), the mean duration of treatment was 610 ± 161 days, which equated to 1262 patient-years in this long-term treatment group.

Adverse events

A higher percentage of patients receiving placebo versus reslizumab 3.0 mg/kg reported 1 or more AEs in the RCTs (81% vs 67%; Table II). When asthma was excluded as an AE, 74% and 63% of patients in the placebo and reslizumab groups, respectively, reported at least 1 (nonasthma) AE.

Asthma (typically recorded using a verbatim term “asthma exacerbation” or occasionally “worsening of asthma”), nasopharyngitis, and upper respiratory tract infection were the most common AEs with both placebo and reslizumab in the RCTs (Table III). These AEs (>5% incidence) occurred at a similar or higher incidence with placebo than with reslizumab. No AEs had an incidence with reslizumab greater than 1% above that with placebo.

Treatment-related AEs were similar in patients in the 2 randomized treatment groups (Table II). Severe AEs affected a higher percentage of patients in the placebo group than in the reslizumab group (10% vs 7%). There were no differences in the AE profiles of reslizumab- or placebo-treated patients according to baseline eosinophil counts (<400 vs ≥ 400 cells/ μ L) or baseline asthma medications (data not shown).

SAEs were reported in 9% of patients receiving placebo (including the death of a 26-year-old man, most probably due to accidental combined drug intoxication with fentanyl and diphenhydramine, which was not considered related to study

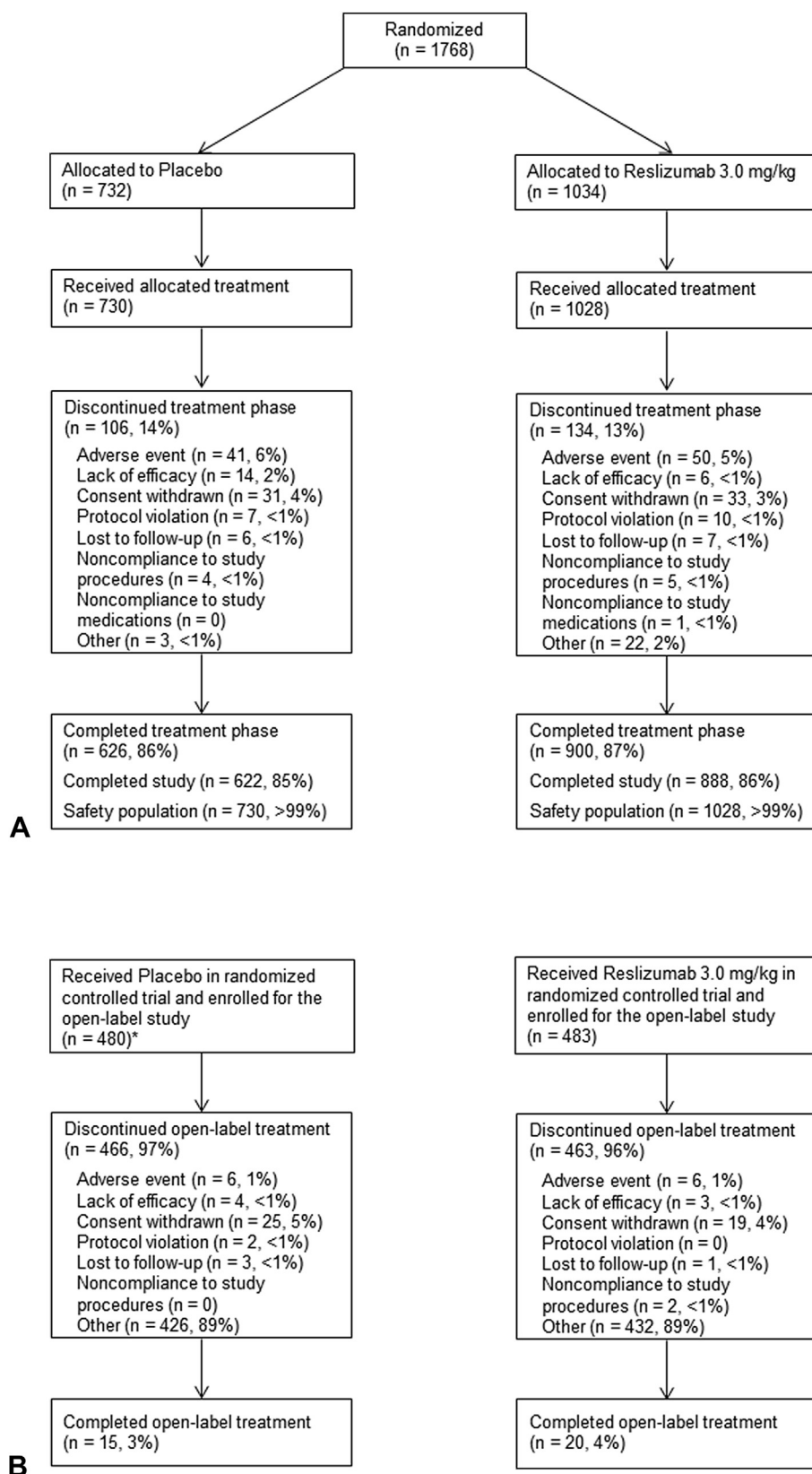


FIGURE 2. Patient disposition in (A) the RCTs and (B) the open-label extension study. Note: The participation of most patients in the open-label study ended at the time of study termination by the study sponsor. *Includes 1 patient who was enrolled for the open-label study but was not treated.

TABLE I. Patients' baseline characteristics in the RCTs

Characteristic	Placebo (n = 730)	Reslizumab 3.0 mg/kg (n = 1028)
Age (y)	46.4 ± 14.1	45.5 ± 13.2
Sex, male, n (%)	276 (38)	388 (38)
Race, n (%)		
White	549 (75)	729 (71)
Black	61 (8)	145 (14)
Asian	57 (8)	79 (8)
American Indian or Alaskan Native	6 (<1)	10 (<1)
Pacific Islander	4 (<1)	1 (<1)
Other	53 (7)	64 (6)
Weight (kg)	78.5 ± 19.3	81.6 ± 21.8
BMI (kg/m ²)	28.3 ± 6.09*	29.4 ± 7.59
FEV ₁ , % predicted	67.4 ± 18.8	67.1 ± 18.3†
Blood eosinophil count (cells/μL)	586 ± 567*	498 ± 504‡
No. (%) of patients with an asthma exacerbation within the last 12 mo	567 (78)	697 (68)
Total daily inhaled corticosteroid dose (μg)§	785 ± 361§	749 ± 368¶
Oral corticosteroid use, n (%)	58 (8)	48 (5)
No. (%) of patients using LABAs	546 (75)	782 (76)
No. (%) of patients using LTRAs	155 (21)	202 (20)

BMI, Body mass index; LABA, long-acting β-agonist; LTRA, leukotriene receptor antagonist.

Data are shown as mean ± SD unless indicated otherwise.

*Data unavailable for 2 patients.

†Data unavailable for 3 patients.

‡Daily inhaled corticosteroid doses are given as fluticasone propionate equivalent doses.

§Data unavailable for 9 patients.

¶Data unavailable for 22 patients.

drug treatment) and 6% of patients treated with reslizumab 3.0 mg/kg (no deaths). Asthma was the most common SAE followed by pneumonia, with similar incidences in both treatment groups in the RCTs (see Table E2 in this article's Online Repository at www.jaci-inpractice.org). SAEs reported by 1 or more patients in the reslizumab group and not reported in the placebo group included anaphylactic reactions, an identified risk of reslizumab treatment. Of the 4 reported SAE anaphylactic events (<1% of reslizumab-treated patients), 1 (reported 45 days after the last reslizumab infusion) was considered to be unrelated to reslizumab and instead due to an immunotherapy injection.

Details of the other 3 events are summarized below (AEs of special interest). Other SAEs reported by 1 or more patients with reslizumab and not with placebo were chest pain (4 patients [<1%] described as chest pain, noncardiac pain, and musculoskeletal chest pain) and falls (2 patients [<1%]). All chest pain cases were assessed as having noncardiac origin; they were not temporally linked to reslizumab infusion (occurring on days 6-16 after infusion), they were fully resolved during the study period, and they were evaluated as not related to reslizumab. The overall incidence (including serious and nonserious events) of falls (2 patients [<1%] in each group) and chest pain (17 patients [2%] in the placebo group and 16 patients [2%] in the reslizumab group) was similar with placebo and reslizumab.

Myalgia, a potential adverse drug reaction with reslizumab, occurred in a small percentage of patients in both treatment

TABLE II. Overview of AEs up to 52 wk in the RCTs

Patients	Placebo (n = 730)	Reslizumab 3.0 mg/kg (n = 1028)	RR (95% CI)
Patients with ≥1 AEs	589 (81)	690 (67)	0.83 (0.79-0.89)
Patients with ≥1 nonasthma AEs	541 (74)	648 (63)	0.85 (0.80-0.91)
Patients with ≥1 SAEs	76 (10)	70 (7)	0.65 (0.48-0.89)
Patients with ≥1 treatment-related AEs	95 (13)	122 (12)	0.91 (0.71-1.17)
Patients who withdrew from a clinical study because of an AE	40 (5)	48 (5)	0.85 (0.57-1.28)
Patients who died	1 (<1)	0	
Patients with ≥1 SAEs	66 (9)	65 (6)	0.70 (0.50-0.97)
Patients with ≥1 treatment-related SAEs	1 (<1)	5 (<1)	3.55 (0.42-30.33)

Data are shown as number (%) of patients.

groups (placebo, 0.55%; reslizumab, 0.97%) and was transient and of mild to moderate severity. One patient in each group withdrew from the study because of myalgia; none of the myalgia cases was associated with any evidence of myositis or rhabdomyolysis.

AEs of special interest

Three anaphylaxis events related to reslizumab infusion occurred in 3 patients. The first of these events occurred in a 45-year-old white woman with asthma with a history of drug hypersensitivity (novaminsulfon allergy and aspirin sensitivity, including anaphylactoid reactions). This patient experienced a reaction 14 minutes after initiation of the second reslizumab 3.0 mg/kg infusion on day 22 of the study, characterized by dyspnea, shivering, vomiting, and flushing. The patient was treated with systemic corticosteroids, antihistamines, and intravenous fluids. The second event occurred on day 36 of the study in a 52-year-old black female patient with asthma with a history of allergic rhinitis but no drug hypersensitivity, shortly after the completion of the second reslizumab 3.0 mg/kg infusion. The anaphylactic reaction presented as shortness of breath, wheezing, inability to speak, swollen eyes, flushing, and oxygen saturation of 89%, and the patient was treated with epinephrine, prednisone, albuterol, and montelukast. The third reslizumab-related anaphylactic reaction was in a 47-year-old white woman with a history of allergies (mold and dog hair sensitivity) and drug hypersensitivities (penicillin and aspirin, including anaphylactoid reactions). This reaction occurred on day 302, shortly after the patient completed the 11th reslizumab 3.0 mg/kg infusion, and the patient experienced skin reactions (pruritus and wheal), severe lower abdominal pain, and severe burning and itching in the genital area with no evidence of circulatory collapse/shock. The patient was treated with systemic corticosteroids, antihistamines, and intravenous fluids. None of the anaphylactic reactions involved respiratory failure or circulatory collapse, and no

TABLE III. AEs with an incidence $\geq 2\%$ among patients receiving reslizumab 3.0 mg/kg by system organ class and preferred term up to 52 wk in the RCTs

Patients	Placebo (n = 730)	Reslizumab 3.0 mg/kg (n = 1028)	RR (95% CI)
AEs by system organ class			
Infections and infestations	386 (53)	420 (41)	0.77 (0.70-0.85)
Respiratory, thoracic, and mediastinal disorders	352 (48)	320 (31)	0.65 (0.57-0.73)
Nervous system disorders	113 (15)	123 (12)	0.77 (0.61-0.98)
Gastrointestinal disorders	108 (15)	109 (11)	0.72 (0.56-0.92)
Musculoskeletal and connective tissue disorders	83 (11)	106 (10)	0.91 (0.69-1.18)
General disorders and administration-site conditions	80 (11)	77 (7)	0.68 (0.51-0.92)
Investigations	59 (8)	73 (7)	0.89 (0.63-1.22)
Skin and subcutaneous tissue disorders	70 (10)	71 (7)	0.72 (0.53-0.99)
Injury, poisoning, and procedural complications	62 (8)	69 (7)	0.79 (0.57-1.10)
Metabolism and nutrition disorders	33 (5)	37 (4)	0.80 (0.50-1.26)
Vascular disorders	19 (3)	32 (3)	1.20 (0.68-2.09)
Psychiatric disorders	21 (3)	21 (2)	0.71 (0.39-1.29)
Eye disorders	25 (3)	19 (2)	0.55 (0.30-0.98)
Cardiac disorders	37 (5)	18 (2)	0.35 (0.20-0.60)
Immune system disorders	16 (2)	17 (2)	0.75 (0.38-1.48)
Ear and labyrinth disorders	11 (2)	16 (2)	1.03 (0.48-2.21)
AEs by preferred term			
Asthma	289 (40)	232 (23)	0.57 (0.49-0.66)
Nasopharyngitis	103 (14)	103 (10)	0.71 (0.55-0.92)
Upper respiratory tract infection	69 (9)	96 (9)	0.99 (0.74-1.33)
Headache	62 (8)	78 (8)	0.89 (0.65-1.22)
Sinusitis	51 (7)	57 (6)	0.79 (0.55-1.14)
Bronchitis	52 (7)	34 (3)	0.46 (0.30-0.71)
Urinary tract infection	24 (3)	34 (3)	1.00 (0.60-1.69)
Back pain	25 (3)	33 (3)	0.94 (0.56-1.56)
Influenza	37 (5)	33 (3)	0.63 (0.40-1.00)
Rhinitis allergic	22 (3)	28 (3)	0.90 (0.52-1.57)
Oropharyngeal pain	16 (2)	27 (3)	1.20 (0.65-2.21)
Pharyngitis	25 (3)	23 (2)	0.65 (0.37-1.14)
Cough	23 (3)	22 (2)	0.68 (0.38-1.21)
Dyspnea	20 (3)	22 (2)	0.78 (0.42-1.42)

Data are shown as number (%) of patients; system organ classes and preferred terms reported in $\geq 2\%$ of patients in the reslizumab 3.0 mg/kg group are presented.

untoward complications or sequelae were observed. All patients affected were discharged home and discontinued from the study. There was no additional evidence of systemic hypersensitivity reactions to reslizumab. Two further reports of anaphylaxis, 1 of which was an SAE, were related to exposure to other allergens (nuts and immunotherapy injection, respectively); these did not result in discontinuation of reslizumab treatment, and both these patients received further infusions without recurrence of symptoms. None of these 5 patients had ADA. Reslizumab-specific IgE antibodies were not detected in patients who reported anaphylactic reactions.

In the RCTs, malignancy was reported in 2 of 730 (0.27%) patients on placebo, compared with 6 of 1028 (0.58%) patients on reslizumab (Table IV). There was no statistically significant between-group difference (difference, 0.31%; 95% CI, -4.43% to 5.05% ; odds ratio, 2.14; 95% CI, 0.38-21.70). The standardized incidence ratio for comparison of the malignancy rate in

the reslizumab group with the external Surveillance, Epidemiology and End Results database was 1.54, but the difference was not statistically significant (95% CI, 0.50-3.58). A diverse range of malignancy types was observed in the RCTs, which would not be unexpected in a primarily adult population (Table IV), and all except 1 (skin squamous cell carcinoma in a patient previously diagnosed with prostate cancer) was diagnosed within less than 6 months from the start of reslizumab treatment.

In the RCTs, infections were more common with placebo than with reslizumab (Table III). The incidence of infections as SAEs was low: 3% in the placebo group and 2% in the reslizumab group. There was no increase in the incidence of infections over time, and no helminth infections or potential opportunistic infections were reported.

In the 4 phase 3 RCTs (studies 2-5; duration 16-52 weeks), ADAs were detected in 53 of 983 (5%) patients with asthma receiving reslizumab 3.0 mg/kg (ADAs were not assessed in

TABLE IV. Malignancies observed in the RCTs

Malignancy	Placebo (n = 730)	Reslizumab 3.0 mg/kg (n = 1028)
Patients with ≥ 1 malignant neoplasms	2 (<1)	6 (<1)
Colon cancer*	1 (<1)	1 (<1)
Keratoacanthoma	0	1 (<1)
Lung adenocarcinoma	0	1 (<1)
Lung neoplasm malignant	0	1 (<1)
Plasmacytoma	0	1 (<1)
Prostate cancer†	0	1 (<1)
Squamous cell carcinoma†	0	1 (<1)
Bladder transitional cell carcinoma	1 (<1)	0
Metastases to liver*	1 (<1)	0
Metastases to lung*	1 (<1)	0

Data are shown as number (%) of patients.

*Patient with colon cancer in the placebo group had metastases to liver and lung.

†Patient had prostate cancer and squamous cell carcinoma.

patients receiving placebo). ADA responses were mostly transient with low titers. AEs were reported in 66% of ADA-negative and 64% of ADA-positive patients. No anaphylactic reactions, systemic hypersensitivity, or immune complex disorders were reported in ADA-positive patients (data not shown). There was also no suggestion that ADA response reduced reslizumab exposure; blood eosinophil levels decreased and FEV₁ improved to a similar extent in ADA-positive and ADA-negative patients (data not shown). The incidence of asthma (preferred term) AEs among ADA-positive patients (12 of 69 [17%]) was numerically lower than among ADA-negative patients (220 of 959 [23%]).

Biochemistry, hematology, and vital signs

Laboratory parameters were similar at baseline in the placebo and reslizumab 3.0 mg/kg groups. As an exception, the mean baseline eosinophil count was higher in the placebo group (586 vs 498 cells/ μ L; RR, 0.60; 95% CI, 0.56-0.64); as stated previously, this might be due to the combination of inclusion criteria and 3:1 active:placebo randomization in study 5 (Table I). In addition, creatine phosphokinase (CPK) levels at baseline were higher in the reslizumab group than in the placebo group (143 vs 132 U/L), and a lower percentage of patients in the reslizumab group versus the placebo group had normal CPK levels at baseline (86% vs 91%).

Except for CPK and eosinophil count, changes from baseline in serum chemistry parameters were generally small, and similar with placebo and reslizumab. Mean CPK levels decreased slightly from baseline with placebo (−4.9 U/L) and increased slightly with reslizumab 3.0 mg/kg (+6.9 U/L). Mean eosinophil count change from baseline was smaller with placebo than with reslizumab (−0.094 and −0.444, respectively; $P < .001$).

There were no clinically meaningful abnormalities and no meaningful changes from baseline in urinalysis variables. ECG values were comparable in patients treated with either placebo or reslizumab.

Concomitant medication

A higher percentage of patients in the placebo group started new medications while in the studies compared with those in the reslizumab group in the RCTs (74% vs 57%; RR, 0.77; 95% CI,

0.72-0.83; see Table E3 in this article's Online Repository at www.jaci-inpractice.org). This difference was most prominent for certain therapies used to treat asthma and/or allergic and infectious comorbidities (particularly systemic corticosteroids, antihistamines, and antibiotics).

Safety of more than 12 months of reslizumab treatment

A subgroup of 756 patients had more than 12 months of exposure to reslizumab 3.0 mg/kg. Of these, 651 (86%) reported 1 or more AEs during treatment (Table V), a greater proportion than in reslizumab-treated patients in the RCTs (67%; ≤ 52 weeks of exposure) but similar to the proportion of patients treated with placebo in the RCTs who experienced AE (81%), which was possibly due to the longer reporting period: the event rate was lower than in the placebo-controlled trials (367.3 events per 100 patient-years for the reslizumab >12-month cohort vs 433.9 for reslizumab and 588 for placebo in the placebo-controlled trials). The proportion of patients having experienced AEs decreased with increasing treatment duration (Figure 3). The same pattern of AEs occurred most frequently with reslizumab exposure for more than 12 months and 52 weeks or less, the most common AE being "asthma" (Table V). SAEs were reported in 12% of patients receiving reslizumab for more than 12 months (Table V). The incidence of treatment-related SAEs was less than 1%.

DISCUSSION

The overall safety profile of reslizumab 3.0 mg/kg every 4 weeks in pooled analyses of 1758 patients was similar to that of placebo, except for rare events of anaphylaxis. The incidence of AEs in patients on treatment for more than 12 months was no higher than in patients with shorter treatment durations. In addition, AE rates were generally lower among patients treated for more than 12 months than in those treated for 52 weeks or less. There was a 23% reduction in concomitant medications in the reslizumab group versus placebo, which may be attributable to a reduced need for asthma treatment because of the therapeutic effects of reslizumab.

A key strength of this analysis was the relatively large patient population, enabling assessment of uncommon safety issues that might not be apparent in single studies. Apart from study 5, which was conducted in the United States only, studies in the analysis were conducted across multiple countries, ensuring a diverse patient population that reflects patients with asthma encountered globally. Areas where parasitic helminthic infections are endemic were also included. In addition, there was no exclusion of patients with prior malignancy, allowing assessment of patients who might be at increased risk of recurrent or new malignancies. However, it should also be acknowledged that the selection criteria for the clinical trials excluded patients with comorbidities such as concurrent immunodeficiency, wherein immune-modifying treatment might constitute a risk. Furthermore, few patients younger than 18 years ($n = 35$ [2%]) were included in the studies, meaning that the results are not necessarily generalizable to a pediatric population. The long-term safety of reslizumab in children with inadequately controlled, moderate to severe asthma with eosinophilia requires additional study. Other limitations of the analysis include minor differences in baseline characteristics between patients receiving reslizumab and those receiving placebo (which may be attributable to the randomization ratio in study 5) and the lack of

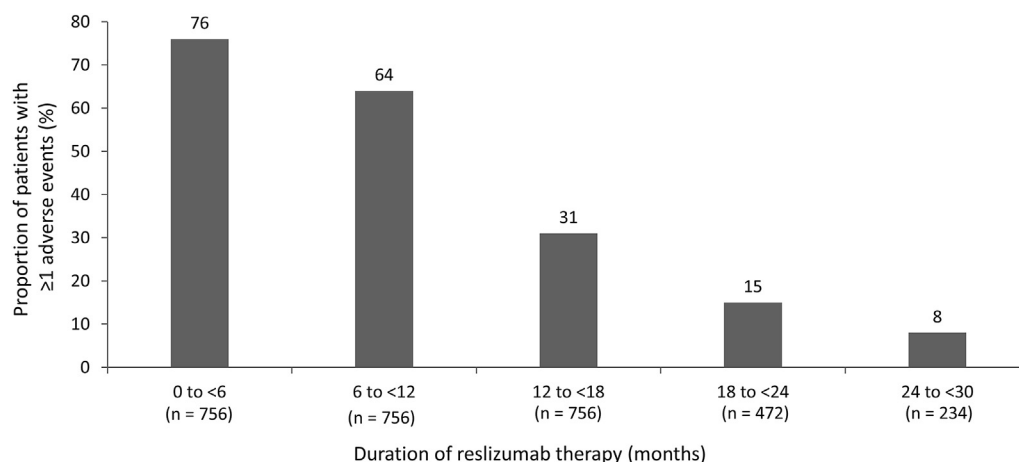
TABLE V. AEs in patients with >12 mo of exposure to reslizumab—comparison with data for ≤12 mo

Patients	Reslizumab 3.0 mg/kg (exposure >12 mo)* (n = 756; 1262 patient-years)		Placebo-controlled trials (≤52 wk)			
	n (%)	Event rate (/100 patient-years)	Placebo (n = 730; 517 patient-years)		Reslizumab 3.0 mg/kg (n = 1028; 612 patient-years)	
			n (%)	Event rate (/100 patient-years)	n (%)	Event rate (/100 patient-years)
Patients with ≥1 AEs	651 (86)	367	589 (81)	588	690 (67)	434
Common AEs (>5% incidence)						
Asthma	320 (42)	58.1	289 (40)	147	232 (23)	69.9
Nasopharyngitis	169 (22)	24.4	103 (14)	29.2	103 (10)	25.0
Upper respiratory tract infection	123 (16)	14.6	69 (9)	19.5	96 (9)	20.9
Headache	104 (14)	12.8	62 (8)	17.2	78 (8)	18.9
Sinusitis	78 (10)	11.4	51 (7)	15.9	57 (6)	12.7
Bronchitis	64 (8)	6.42	52 (7)	12.8	34 (3)	6.20
Influenza	54 (7)	6.10	37 (5)	9.87	33 (3)	6.86
Patients with ≥1 SAEs	87 (12)	11.8	66 (9)	21.1	65 (6)	17.0
AEs leading to discontinuation	8 (1)	0.871	40 (5)	11.61	48 (5)	8.65
AEs of special interest						
Infections and infestations	506 (67)	121	386 (53)	163	420 (41)	130
Anaphylactic reaction	1 (<1)†	0.079	0	0	5 (<1)‡	0.816
Malignancy	12 (2)	1.188	2 (<1)	0.387	6 (<1)	1.143
Myalgia	10 (1)	0.792	4 (<1)	1.16	10 (<1)	1.63

*Data represent all reported AEs in this patient cohort, regardless of when the AEs occurred. For patients who received placebo during the randomized controlled trials, AEs occurring during placebo treatment are excluded.

†Patient with anaphylactic reaction to immunotherapy injection during the placebo-controlled trials continued into the open-label extension (study 6).

‡Of the 5 anaphylactic reactions reported in the placebo-controlled trials, 3 were temporally linked to reslizumab infusion and resulted in permanent discontinuation of reslizumab treatment. Two cases (1 reported as nonserious) occurred after exposure to nuts and immunotherapy injection, respectively; these were not considered to be related to reslizumab infusion, and they did not reoccur with subsequent reslizumab infusions. There were no cases of anaphylaxis during the open-label extension study.

**FIGURE 3.** Proportion of patients experiencing 1 or more AEs according to the duration of reslizumab therapy among patients (n = 756) who received more than 12 months of reslizumab treatment. Data shown are for patients who received more than 12 months of treatment with reslizumab (n = 756).

any comparator treatment for patients receiving reslizumab for more than 12 months. While acknowledging these limitations, however, it should be recognized that this analysis provides a useful update of the safety profile of reslizumab from a relatively large population of patients with asthma.

Meta-analyses have recently reported safety data for reslizumab with similar results: one of them found similar percentages of withdrawals due to AEs on reslizumab or placebo; the most common AEs with reslizumab affected the upper respiratory tract.¹² In an analysis of 3 anti-IL-5 drugs, only reslizumab

demonstrated a significantly reduced risk of AEs versus placebo (RR, 0.88; 95% CI, 0.81-0.96).¹⁶

Although anaphylactic reactions are uncommon, appropriate precautions should be taken when reslizumab is administered. As further information regarding the potential for severe hypersensitivity reactions is gained through additional clinical studies and postmarketing surveillance of reslizumab, it may become clearer whether reslizumab rechallenge may be appropriate for some patients. Infections occurred at a similar or lower incidence with reslizumab than with placebo, and were consistent with those commonly reported among individuals with asthma. No helminthic parasitic infections or opportunistic infections were reported. Development of ADAs against reslizumab was rare, and was not associated with anaphylaxis or other clinically adverse effects, and reslizumab-specific IgE antibodies were not observed among any of the patients who experienced anaphylaxis. Furthermore, the safety profile of reslizumab was not different between ADA-positive and ADA-negative patients.

Regarding the nonsignificant imbalance between reslizumab and placebo in the incidence of malignancies (0.58% vs 0.27%), there are several important considerations. First, the number of events in both groups is small, with an even smaller frequency of placebo-treated individuals, which may have contributed to this apparent imbalance, particularly because preclinical studies have created no suggestion that reslizumab is carcinogenic.⁸ Furthermore, the observed malignancies were common and diverse types, as is typical in a normal adult population. All except 1 of the malignancies in patients receiving reslizumab in the placebo-controlled trials were diagnosed within 6 months of starting treatment, suggesting that these malignancies may have been undiagnosed before entry into the study. Comparison of the placebo-controlled trial data with the Surveillance, Epidemiology and End Results database showed no significant increase in the risk of malignancies with reslizumab versus the general population. As with any agent with immunomodulatory effects, ongoing postmarketing surveillance to detect rare malignancies and other potential tolerability issues remains essential.

CONCLUSIONS

This pooled analysis, with treatment periods exceeding 12 months in many patients, confirms previous reports from individual studies indicating that reslizumab is well tolerated in patients with asthma and eosinophilia. No new tolerability or safety issues were observed. Incidence of any specific AE in reslizumab-treated patients did not exceed that in the placebo group by more than 1%. The incidence of AEs in patients on treatment for more than 12 months was no higher than in patients with shorter treatment durations. Three cases of anaphylaxis occurred with reslizumab and were managed with standard therapies with no untoward complications or sequelae. A nonsignificant imbalance between reslizumab and placebo was observed in the incidence of malignancy, without evidence to suggest that these malignancies were associated with reslizumab.

The incidence of ADA positivity was low and not associated with clinical sequelae.

Acknowledgments

Medical writing support was provided by Matt Brierley, PhD, and Dawn L. Lee, PhD, of GeoMed, an Ashfield company, part of UDG Healthcare plc, and was funded by Teva Branded Pharmaceutical Products R&D, Inc (Malvern, Pa), during the preparation of this manuscript. Teva provided a full review of the article. The authors were fully responsible for all content and editorial decisions, were involved at all stages of manuscript development, and have approved the final version.

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TABLE E1. Key inclusion criteria for studies in the analysis

Study	Inclusion criteria
Study 1 (phase 2)	• Age 18-75 y • Asthma with eosinophilia (sputum eosinophils $\geq 3\%$) • Treatment with high-dose ICSs and at least 1 other agent • Poorly controlled disease (ACQ score ≥ 1.5)
Study 2 (phase 3)	• Age 12-75 y • Persistent asthma with eosinophilia (blood eosinophil levels ≥ 400 cells/μL) • Treatment with at least a medium dose of ICS, with or without another controller agent • Poorly controlled disease (ACQ score ≥ 1.5)
Studies 3 and 4 (phase 3)	• Age 12-75 y • Moderate to severe asthma with eosinophilia (blood eosinophil levels ≥ 400 cells/μL) • Treatment with at least a medium dose of ICS, with or without another controller agent • Poorly controlled disease (≥ 1 asthma exacerbations treated with a systemic corticosteroid within the past 12 mo and ACQ score ≥ 1.5)
Study 5 (phase 3)	• Age 18-65 y • Asthma (with or without eosinophilia) • Treatment with at least a medium dose of ICS, with or without another controller agent • Poorly controlled disease (ACQ score ≥ 1.5)
Study 6 (open-label extension)	• Completed study 2, 3, or 4

ACQ, Asthma Control Questionnaire; ICS, inhaled corticosteroid.

TABLE E2. SAEs in the RCTs, by preferred term

SAE	Placebo (n = 730)	Reslizumab 3.0 mg/kg (n = 1028)
Patients with ≥ 1 SAEs	66 (9)	65 (6)
Asthma*	23 (3)	23 (2)
Pneumonia	7 (<1)	7 (<1)
Anaphylactic reaction	0	4† (<1)
Chest pain	0	2 (<1)
Fall	0	2 (<1)
Road traffic accident	3 (<1)	2 (<1)
Sinusitis	2 (<1)	2 (<1)
Urinary tract infection	2 (<1)	0
Contusion	2 (<1)	0
Bronchitis	2 (<1)	0

Data are shown as number (%) of patients; SAEs reported in ≥ 2 patients in either treatment group are shown.

*Asthma SAEs indicate asthma exacerbations that would have resulted in hospitalization.

†One case was an anaphylaxis reaction related to immunotherapy injection.

TABLE E3. Concomitant medications by therapeutic class, started after baseline in the RCTs

Medication	Placebo (n = 730)	Reslizumab 3.0 mg/kg (n = 1028)	RR (95% CI)
Patients receiving concomitant medications*	540 (74)	587 (57)	0.77 (0.72-0.83)
Antibacterials for systemic use	287 (39)	264 (26)	0.65 (0.57-0.75)
Corticosteroids for systemic use	271 (37)	216 (21)	0.57 (0.49-0.66)
Analgesics	161 (22)	185 (18)	0.82 (0.68-0.99)
Drugs for obstructive airway diseases	146 (20)	117 (11)	0.57 (0.45-0.71)
Antihistamines for systemic use	117 (16)	104 (10)	0.63 (0.49-0.81)
Cough and cold preparations	93 (13)	99 (10)	0.76 (0.58-0.99)
Nasal preparations	95 (13)	89 (9)	0.67 (0.51-0.87)
Anti-inflammatory and antirheumatic products	84 (12)	98 (10)	0.83 (0.63-1.09)
Drugs for acid-related disorders	63 (9)	37 (4)	0.42 (0.28-0.62)

Data are shown as number (%) of patients; concomitant medications reported by $\geq 5\%$ of patients in either treatment group are shown.

*New concomitant medications started during the treatment period.