Nasal IL-5 levels determine the response to anti–IL-5 treatment in patients with nasal polyps

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Background: Chronic rhinosinusitis with nasal polyps is characterized by an eosinophilic inflammation and high IL-5 levels.
Objectives: Antagonizing the effect of IL-5 is a potential new treatment strategy in patients with nasal polyps.
Methods: In a double-blind, placebo-controlled, randomized, 2-center safety and pharmacokinetic study, 24 subjects with bilateral nasal polyps were randomized to receive a single intravenous infusion of reslizumab, a humanized anti-human IL-5 mAb, at 3 mg/kg or 1 mg/kg or placebo. We evaluated the safety and pharmacokinetics of reslizumab, and biologic activity was assessed by means of endoscopic evaluation of polyp size, symptoms, peripheral eosinophil counts, peripheral and local IL-5 levels, eotaxin levels, and eosinophil cationic protein levels.
Results: We demonstrated that a single injection of reslizumab up to 3 mg/kg is safe and well tolerated. Blood eosinophil numbers and concentrations of eosinophil cationic protein were reduced up to 8 weeks after treatment in serum and nasal secretions. Individual nasal polyp scores improved only in half of the treated patients for 4 weeks. Responders had increased IL-5 concentrations in nasal secretions at baseline compared with nonresponders, and logistic regression analysis revealed that increased nasal IL-5 levels (>40 pg/mL) predict the response to anti-IL-5 treatment.
Conclusion: A single injection of anti–IL-5 reduces the size of nasal polyps for 4 weeks in half of the patients, and nasal IL-5 levels predict the response to anti–IL-5 treatment.
Clinical implications: Intravenous administration of a humanized anti-human IL-5 mAb is safe and reduces the size of nasal polyps in half of the patients. (J Allergy Clin Immunol 2006;118:1133-41.)

Key words: *Chronic rhinosinusitis, nasal polyps, eosinophils, IL-5, IL-5 receptor α, anti–IL-5*

Chronic rhinosinusitis with bilateral nasal polyps (NP) affects 4.3% of the population and is frequently associated with asthma. NP is characterized by an abundance of eosinophils in more than 80% of cases.[1,2] The role of eosinophils in this disease is not clear, and its clarification awaited the availability of a specific drug approach that would not, like topical or systemic glucocorticosteroids, affect a wide range of cells and mediators. IL-5 is essential for terminal differentiation of the committed eosinophil precursor but also activates and prolongs survival of the mature cells in tissues and represents a specific therapeutic target.[3,4] IL-5 was found to be significantly increased in patients with NP compared with in healthy control subjects and patients with other forms of sinusitis.[5,6] The highest concentrations of IL-5 were found in NP tissue of subjects with nonallergic asthma and aspirin sensitivity, conditions linked to severe tissue eosinophilia. The key role of IL-5 was supported by the finding that treatment of eosinophil-infiltrated polyp tissue with neutralizing anti–IL-5 mAb, but not anti–IL-3 or anti-GM-CSF mAbs, resulted in eosinophil apoptosis and decreased tissue eosinophilia *in vitro*.[7] However, as in asthma, only antagonizing the effect of IL-5 in nasal polyposis *in vivo* would be the ultimate test of the IL-5/eosinophil hypothesis.[8]

Asthma was, indeed, long the main target of anti–IL-5 treatment. Several clinical trials with humanized mAbs against IL-5 in subjects with mild-to-severe asthma demonstrated depletion of blood and sputum eosinophils but no effect on airway hyperresponsiveness or the late asthmatic reaction to inhaled allergen challenge.[9-12] However, anti–IL-5 therapy effectively controlled eosinophilic dermatitis and reduced blood and tissue eosinophilia in patients with hypereosinophilic syndrome.[13,14] At the local tissue level, strategies to antagonize IL-5 might have to face unexpected difficulties because it was demonstrated that in bronchoalveolar lavage–derived eosinophils from asthmatic subjects[15,16] and in nasal polyp tissue, the membrane-anchored IL-5Rα isoform is downregulated, whereas the soluble IL-5Rα (SOL IL-5Rα) variant (antagonistic) is upregulated compared with levels seen in peripheral blood.[6]

As a target tissue for measuring the effect of anti–IL-5 treatment on eosinophilic inflammation, nasal polyps have

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TABLE I. Baseline characteristics

	Placebo (n = 8)	Reslizumab (SCH55700) 1 mg/kg (n = 8)	Reslizumab (SCH55700) 3 mg/kg (n = 8)
Age (y [range])	48 (21-59)	43.6 (22-63)	48.5 (18-57)
Female/male sex	2/6	2/6	4/4
Asthma in history	6	7	5
Nasal surgery in history	4	2	6
Total nasal polyp score (range)	6.00 (4.5-8.0)	6.00 (4.5-7.0)	5.00 (3.5-6.75)
Blood/serum*			
Blood eosinophils (10^3/mL)	0.17 (0.13-0.28)	0.21 (0.18-0.35)	0.24 (0.18-0.46)
ECP (μg/L)	10.7 (5.2-34.7)	15.8 (11.2-35.7)	13.5 (9.9-31.6)
Eotaxin (pg/mL)	158.8 (118.3-172.5)	166.8 (135.6-203.1)	141.9 (125.6-185.8)
SOL IL-5Rα (pg/mL)	547 (406-756)	464.6 (384-695)	737 (436-2263)
Nasal secretion*			
ECP (μg/L)	344.1 (74.2-867.3)	350.7 (76.6-1519.6)	283.1 (196.8-932.1)
IL-5 (pg/mL)	34.9 (24.6-138.0)	39.5 (24.5-292.7)	45.2 (26.3-61.1)
Eotaxin (pg/mL)	344.4 (227.7-614.3)	672.5 (261.8-1401.6)	243.1 (163.6-654.2)
SOL IL-5Rα (pg/mL)	1385 (677-3766)	2243 (779-6461)	2198 (592-7103)

*Median (interquartile range).

Abbreviations used
ECP: Eosinophil cationic protein
NP: Chronic rhinosinusitis with bilateral nasal polyps
SOL IL-5Rα: Secreted IL-5Rα

the advantage of being easily visualized by means of nasal endoscopy and are accessible for the measurement of IL-5, SOL IL-5Rα, eotaxin, and eosinophil cationic protein (ECP) levels.[6] Furthermore, it is possible to determine whether anti-IL-5 treatment affects tissue eosinophilic inflammation without the confounding effects of corticosteroids required by most subjects with persistent asthma.

The primary objective of this study was to determine the safety and pharmacokinetics of reslizumab (SCH55700) administered as a single intravenous dose of 3 mg/kg to subjects with severe nasal polyposis. In addition, the activity of reslizumab on the clinical course of severe nasal polyps and on peripheral and nasal eosinophilic inflammation was evaluated.

METHODS

Patients

Twenty-four subjects with massive bilateral nasal polyps (grade 3 or 4, see ''Outcome measures'' section) or recurrent nasal polyps after surgery were included. The baseline characteristics were comparable between treatment groups (Table I), with the exception of sex, with male subjects outnumbering female subjects. Two subjects had a history of aspirin hypersensitivity. The exclusion criteria specified that the use of systemic corticosteroids was not allowed during the last month before treatment, whereas subjects were not permitted to use systemic and nasal corticosteroids, nasal antihistamines, nasal atropine, nasal cromolyn, nasal saline, and antibiotic treatment up to 2 months after dosing. The study was conducted at the Departments of Otorhinolaryngology of the University Hospitals in Ghent, Belgium, and in Graz, Austria. The local ethics committees approved the study, and all volunteers provided written informed consent before participation in the study.

Study design

This is a phase I, single-dose, randomized, double-blind, placebo-controlled, 3-arm, parallel-group, 2-center safety and pharmacokinetic study of reslizumab in patients with nasal polyps. After a 1- to 2-week run-in period, subjects were randomized to receive treatment with reslizumab (Schering-Plough Research Institute, Kenilworth, NJ) at 3 mg/kg or 1 mg/kg or placebo. A single dose was administered as an intravenous infusion over 30 minutes in a double-blind fashion. Subjects were confined to the study site for 24 hours after dosing for safety evaluations and collection of samples for pharmacokinetic analyses. Follow-up visits were scheduled 48 hours after dosing and 1, 2, 4, 8, 12, 16, 20, 24, 28, 32, and 36 weeks after dosing.

Outcome measures

Safety was assessed on the basis of adverse event reporting, vital signs, symptom check, physical examination, electrocardiography, and blood and urine analysis. The key efficacy variable was the nasal polyp score evaluated for each nostril by means of nasal endoscopy. Polyps were graded based on polyp size: grade 0, no polyps; grade 1, small polyps in the middle meatus not reaching below the inferior border of the middle concha; grade 2, polyps reaching below the lower border of the middle turbinate; grade 3, large polyps reaching the lower border of the inferior turbinate or polyps medial to the middle concha; and grade 4, large polyps causing complete obstruction of the inferior meatus. Throughout the article, the total nasal polyp score is used, which is the sum of the right and left nostril scores. Furthermore, nasal peak inspiratory flow measurements and symptoms (anterior rhinorrhea, nasal obstruction, postnasal drip, and loss of sense of smell) were recorded. Biologic activity was evaluated on the basis of peripheral blood eosinophil counts and peripheral blood and nasal secretion (local) of IL-3, IL-5, SOL IL-5Rα, eotaxin, ECP, and GM-CSF.[6]

Blood eosinophil counts were automated on a 2-mL heparinized blood sample. Nasal secretions were obtained by placing sinus packs (IVALON 4000 plus 3.5 × 0.9 × 1.2 cm surgical products M-Pact, Eudora, Kan) in both nasal cavities for exactly 5 minutes. All freshly obtained nasal secretion and serum samples were immediately

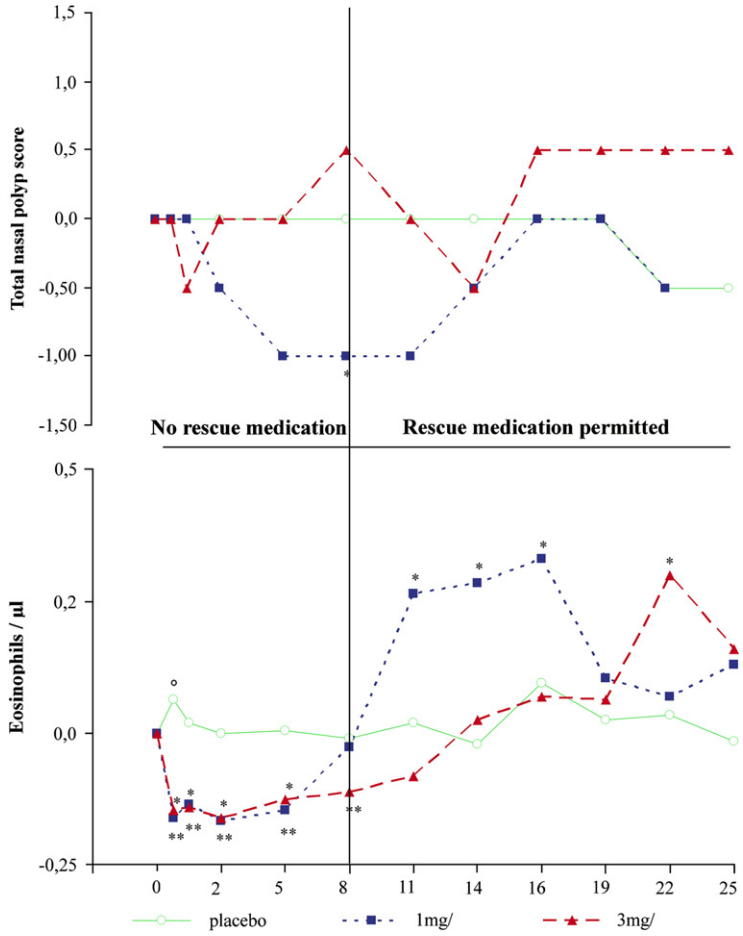

FIG 1. The effect of a single dose of reslizumab at 1 mg/kg (n = 8; *solid squares*) or 3 mg/kg (n = 8; *solid triangles*) versus placebo (n = 8; *open circles*). The median changes from baseline were significantly different in the placebo group *(°)*, the 1 mg/kg group *(*)*, and the 3 mg/kg group *(**)*.

processed, separated, and stored in aliquots at −20°C until analysis, as previously described.[6] Serum and nasal secretions were assayed by means of ELISA for SOL IL-5Rα (Innogenetics, Ghent, Belgium), eotaxin, GM-CSF, IL-3, and IL-5 (R&D Systems, Minneapolis, Minn).[6] ECP concentrations were measured by using the Uni-CAP system (Pharmacia & Upjohn, Uppsala, Sweden).

Statistical analysis

Analyses of safety and efficacy were based on the data collected from all subjects randomized in the study (intention-to-treat population). Statistical analysis of efficacy was based on all randomized subjects. However, 2 subjects, both in the placebo group, had undergone sinus surgery because of unbearable symptoms, and their polyps were removed during the treatment period. Therefore additional analysis, excluding postnasal surgery data, was performed where applicable. Missing observations were replaced by the last nonmissing observation carried forward. Data are expressed as medians and interquartile ranges. When comparisons were made between groups, significant between-group variability was first established by using the Kruskal-Wallis test. The Mann-Whitney *U* test was then used for comparison between the treatment groups. Differences between the baseline visit and the visits after dosing were calculated by using the Wilcoxon test. Differences were regarded as statistically significant at a *P* value of less than .01 to correct for serial testing.

We performed logistic regression analysis to identify independent predictors of rebound and response after anti-IL-5 treatment. Differences were regarded as statistically significant at a *P* value of less than .05.

RESULTS

Safety and adverse events

Twenty-three (95.8%) of the 24 subjects reported at least 1 adverse event. The 1 subject who did not report an adverse event was in the 3.0 mg/kg treatment group. In 2 subjects, both in the placebo group, nasal surgery with removal of the nasal polyps was indicated during the treatment period. The most common adverse event was upper respiratory tract infection, which was reported by a total of 14 (58.3%) subjects, 5 in each of the treatment groups and 4 in the placebo group. Examination of other adverse events did not reveal any major differences between treatment groups. Administration of a single dose of reslizumab was well tolerated, and no clinically meaningful changes were observed in laboratory parameters, vital signs, or physical examinations in any of the treatment groups.

TABLE II. Clinical course of nasal polyps

Total nasal polyp score compared with baseline score is:	Placebo (n = 8)			Reslizumab (SCH55700) 1 mg/kg (n = 8)			Reslizumab (SCH55700) 3 mg/kg (n = 8)		
	Worse	No change	Better	Worse	No change	Better	Worse	No change	Better
Wk 1	3	4	1	1	4	3	0	5	3
Wk 2	3*	4	1	0	5	3	0	4	4
Wk 4	3	3	2	0	4	4	0	5	3
Wk 8	3*	4	1	1	2	5	3	4	1
Wk 12	3	2	3	1	2	5	4	3	1

The number of subjects who had a better, an unchanged, or a worse total nasal polyp score compared with individual baseline score is shown. Eight subjects in the treated groups showed an improvement of 1 unit within 4 weeks after dosing and were identified as responders.
*Nasal surgery with removal of the nasal polyps was indicated in 2 subjects.

Clinical efficacy analysis

At no individual time point was there a significant difference in the symptom scores or in the nasal peak inspiratory flow values in both treatment groups compared with those in the placebo group. The total nasal polyp score was only significantly decreased in the 1 mg/kg group at week 12 compared with baseline values (Fig 1). However, this study was not designed and not powered to detect treatment differences in efficacy variables. Therefore the individual clinical course was evaluated and expressed as the number of subjects who had a better, an unchanged, or a worse total nasal polyp score compared with the individual baseline score (Table II and Fig 2). Treatment with 1 mg/kg reslizumab improved the nasal polyp scores up to 12 weeks in 5 of 8 subjects. In the 3 mg/kg treatment group 4 of 8 patients had a better nasal polyp score up to 4 weeks after treatment; however, there was a deterioration of the nasal polyp score in 4 subjects 12 weeks after receiving reslizumab. In the placebo group 3 patients had worse nasal polyp scores, of whom 2 patients required nasal surgery at 2 and 11 weeks, and 1 patient had a better nasal polyp score. Systemic and nasal corticosteroids were permitted after 8 weeks and were used in 7 and 20 of 24 patients, respectively, with an equal distribution over the 3 groups and follow-up visits (from 12 to 36 weeks). Further analysis was mainly focused on the first 12 weeks after dosing to avoid bias by concomitant treatment.

Biologic activity analysis

Reslizumab induced a significant decrease in blood eosinophil counts in both treatment groups compared with the placebo group as early as 12 hours after dosing, which was sustained through week 8 after dosing (Fig 1). Blood eosinophil counts returned to baseline levels at week 12. However, a significant rebound eosinophilia was noted at week 24 and week 32 after 1 mg/kg and 3 mg/kg treatment, respectively (Fig 1). Rebound eosinophilia with a more than 100% increase of baseline eosinophil numbers was present in 6 and 4 patients of the 1 mg/kg and 3 mg/kg treatment groups, respectively. Serum ECP and SOL IL-5Rα levels decreased significantly up to 4 weeks in both treatment groups compared with the placebo group and paralleled the blood eosinophil counts but did not show a significant rebound at later time points (Fig 3, *A*). There were no significant differences in eotaxin concentrations in the serum and nasal secretions throughout the study (Fig 3). The concentrations of IL-3 and GM-CSF in serum and nasal secretions were under the detection limit in almost all subjects (data not shown).

Nasal secretion levels of ECP and SOL IL-5Rα decreased in both groups receiving reslizumab compared with placebo and were sustained through week 8 (Fig 3, *B*). Nasal IL-5 concentrations were significantly suppressed at week 2 in both treatment groups versus the placebo group.

There is a significant increase of blood eosinophil counts, serum SOL IL-5Rα levels, and ECP levels in nasal secretions and in serum up to 1 week after dosing in the placebo group (Fig 3). We believe that it is a systemic effect induced by repetitive blood withdrawal for assessing safety.

Responders versus nonresponders

Based on the individual course of the total nasal polyp score, all treated patients with an improvement of 1 unit within 4 weeks after dosing were sorted into responders (n = 8) and nonresponders (n = 8; Fig 2). In a post-hoc analysis the total nasal polyp score was significantly decreased in responders from 1 to 8 weeks after treatment compared with baseline values. At baseline, the nasal scores and biologic markers were comparable between the groups, with the exception of IL-5 levels in nasal secretions, which were significantly higher in the responders than in the nonresponders ($P = .027$, Table III). Logistic regression analysis revealed that increased nasal IL-5 levels (>40 pg/mL) predict the response to anti–IL-5 treatment (odds ratio, 21.0; 95% CI, 1.5-293.3; $P = .009$), whereas no other variables could be retained in the model. Nasal IL-5 concentrations decreased significantly within 7 days after dosing and were sustained through week 2 after dosing in the responders (Fig 4), whereas they increased in the nonresponders, reaching significance within 12 to 20 weeks after active treatment. The decrease in nasal ECP levels was significant at 1, 4, and 12 weeks after dosing in the responders (Fig 4). There was a significant decrease in blood eosinophil counts and SOL IL-5Rα concentrations in serum and nasal secretions in both treated groups compared with baseline value (similar to Fig 1),

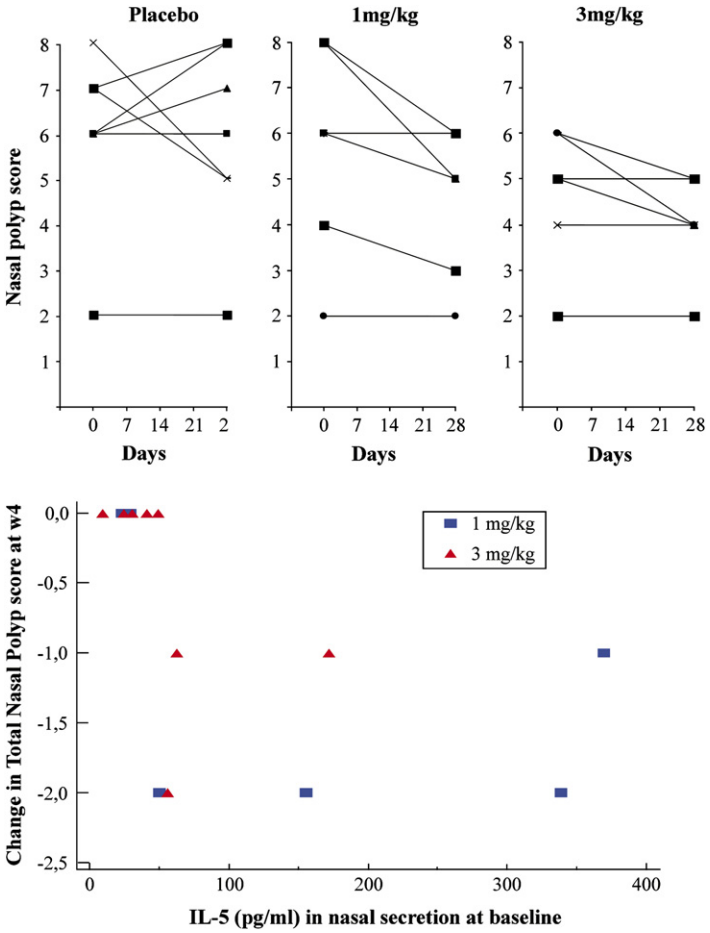

FIG 2. Individual nasal polyp scores at baseline and at 4 weeks after treatment with a single dose of reslizumab and individual nasal IL-5 concentrations at baseline versus change in nasal polyp scores at 4 weeks after treatment with a single dose of reslizumab.

without a significant difference between responders and nonresponders (data not shown).

DISCUSSION

This study demonstrates that administration of a single dose of reslizumab, a humanized anti-human IL-5 mAb, at 3 mg/kg is safe and well tolerated in subjects with nasal polyposis. Individual nasal polyp scores improved only in half of the verum-treated patients for up to 4 weeks. When carefully analyzing responders and nonresponders in a post-hoc analysis, only those nasal polyps with increased levels of IL-5 (>40 pg/mL) in nasal secretions before treatment seemed to benefit from anti–IL-5 treatment. Furthermore, nasal IL-5 levels decreased only in the responders, whereas they increased in the nonresponders. The decrease in circulating blood eosinophil counts was as pronounced in responders as in nonresponders and was sustained for 8 weeks, whereas the decrease in nasal ECP levels was stronger in responders but lasted for 1 week only. These data show that at least in 50% of the nasal polyps, IL-5 and eosinophils play a key role (IL-5 dependent) in sustaining polyp size, whereas in the rest eosinophilia might be dependent on other factors (IL-5 independent).[17]

Analysis of anti–IL-5 studies in animal models of allergic disease shows that although it has been observed that eosinophil trafficking to the allergic mucosa is markedly attenuated in IL-5$^{-/-}$ mice or those treated with anti–IL-5 antibodies in comparison with wild-type responses, a marked residual tissue eosinophilia can persist in these mice after allergen inhalation.[18-21] Indeed, in a clinical trial Flood-Page et al[9,10] observed a significant differential effect of IL-5 blockade on eosinophil counts in various body compartments. After multiple dosing with mepolizumab, another anti–IL-5 mAb, the authors found 100% reduction in blood eosinophil counts but only 52% reduction in the bone marrow and a 55% decrease in the bronchial mucosa.[10] A possible reason for a different effect of anti–IL-5 in one compartment as opposed to another might be poor penetration of anti–IL-5 into the tissues or a varying IL-5 sensitivity caused by a different expression of the IL-5Rα isoforms according to activation state, maturation, and localization in the body. Liu et al[15,16] showed that IL-5 receptor expression on airway eosinophils was downregulated *in vivo* after inhaled allergen challenge,

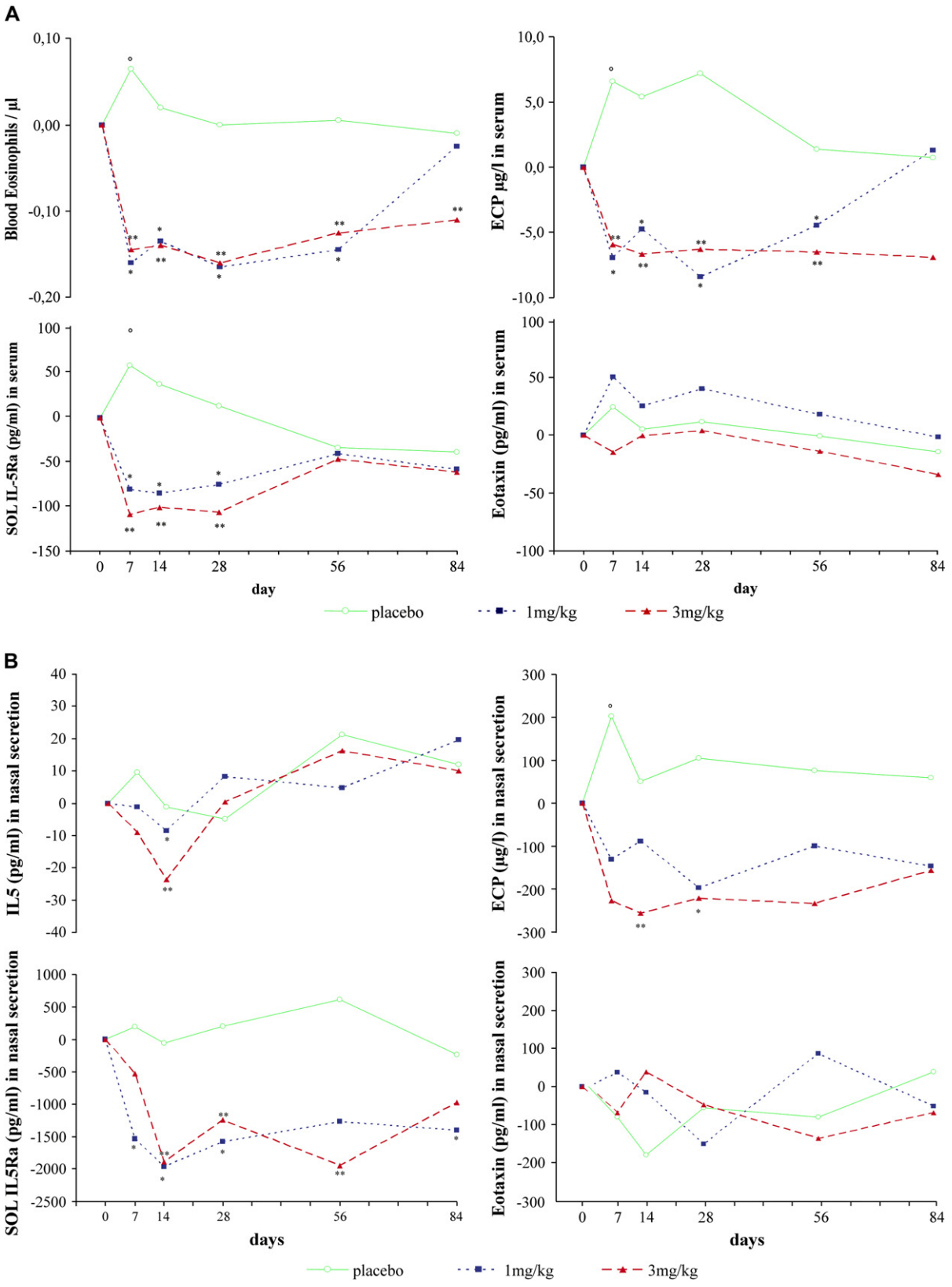

FIG 3. The effect of a single dose of reslizumab on blood/serum eosinophilic markers **(A)** and on tissue eosinophilic markers **(B)**. The median changes from baseline were significantly different in the placebo group *(°)*, the 1 mg/kg group *(*)*, and the 3 mg/kg group *(**)*.

TABLE III. Comparison of baseline characteristics: Responders versus nonresponders

	Reslizumab (SCH55700) at 1 mg/kg or 3 mg/kg		
	Nonresponders (n = 8)	***P* value**	**Responders (n = 8)**
Age (y [range])	48 (33-63)	.596	42 (18-57)
Sex (female/male)	4/4	.608	2/6
Asthma in history	6	1	6
Sinus surgery in history	5	.619	3
Total nasal polyp score (range)	4.5 (2-6)	.176	5.5 (4-7)
Blood/serum*			
Blood eosinophils (10^3/mL)	0.22 (0.18-0.60)	.674	0.24 (0.16-0.32)
ECP (μg/L)	23.5 (12.0-38.9)	.141	11.7 (10.2-18.4)
Eotaxin (pg/mL)	169.2 (128.5-186.9)	.636	149.9 (123.2-200.8)
SOL IL-5Rα (pg/mL)	573.2 (424.5-917.4)	.529	587.5 (309.2-755.9)
Nasal secretion*			
ECP (μg/L)	264.0 (97.8-676.7)	.345	420.6 (133.0-1628.2)
IL-5 (pg/mL)	27.6 (24.1-44.4)	.027	109.2 (43.5-295.8)
Eotaxin (pg/mL)	266.4 (155.4-383.9)	.093	852.7 (212.8-1401.6)
SOL IL-5Rα (pg/mL)	4123 (765-6808)	.529	2320 (1285-5506)

*Median (interquartile range).

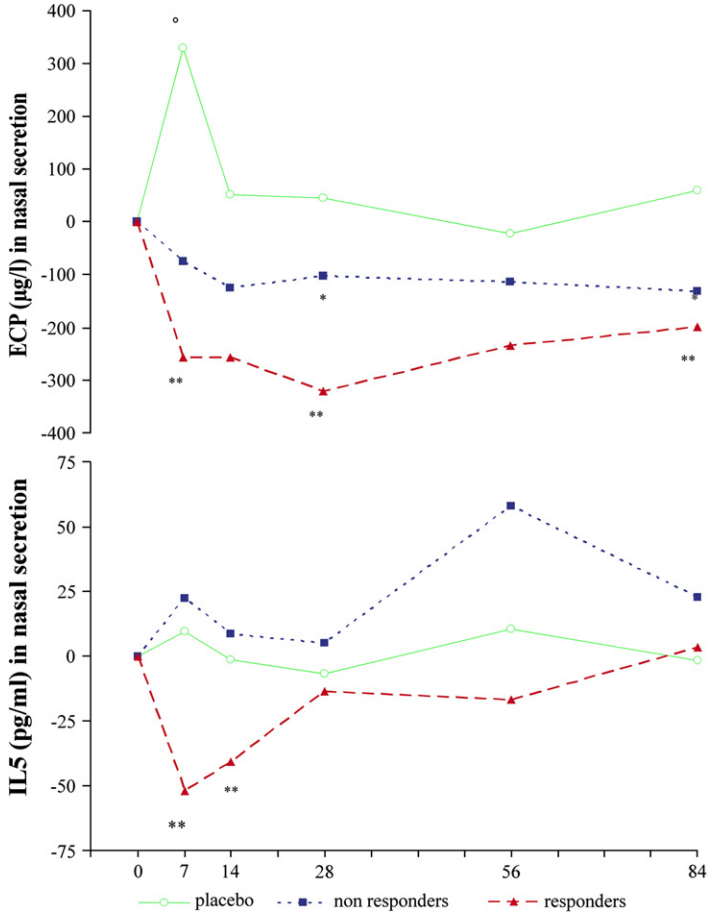

FIG 4. ECP and IL-5 concentrations in nasal secretion responders (n = 8; *solid triangles*) and nonresponders (n = 8; *solid squares*). The total nasal polyp score and concentrations of IL-5 in nasal secretions were significantly decreased in responders compared with in nonresponders. The median changes from baseline were significantly different in the nonresponders *(*)* and in the responders *(**)* compared with baseline values.

which was associated with a loss of IL-5 responsiveness. In addition, Gregory et al[22] have demonstrated that exposure of blood eosinophils to IL-3, IL-5, or GM-CAF *in vitro* leads to sustained downregulation of SOL IL-5Rα expression and reduced responsiveness to IL-5 but no sustained changes in CCR3 expression. Analysis of nasal tissue samples revealed that SOL IL-5Rα protein and mRNA levels were significantly increased in polyp versus control tissue, whereas the membrane-anchored IL-5Rα expression was downregulated in polyp tissue with severe eosinophilia.[6] Here we demonstrate that anti–IL-5 treatment of patients with NP reduced SOL IL-5Rα levels for several weeks, especially in nasal secretions. Because SOL IL-5Rα shows antagonistic activity *in vitro*,[23-26] it could theoretically be expected that assessment of endogenous SOL IL-5Rα levels might distinguish responders from nonresponders or help in the titration of anti–IL-5 mAb therapy.[6] However, SOL IL-5Rα levels did not show any relation to the individual response in this safety study in patients with NP. In line with previous studies, IL-3 and GM-CSF concentrations were not detectable in nasal polyp samples.[5] Increased eotaxin concentrations were found in serum and in nasal secretions of all patients with NP but were not related to response. In contrast, local IL-5 concentrations predicted the response: only patients with NP with increased nasal IL-5 showed a reduction of nasal polyp scores after a single dose of reslizumab.

A heterogeneous group of disorders characterized by the presence of unexplained blood eosinophilia is the hypereosinophilic syndrome. Two reports showed successful treatment of patients with mepolizumab and reslizumab.[13,14] Anti–IL-5 therapy effectively controlled eosinophilic dermatitis, with a decrease in eosinophil counts and IL-5, eotaxin, and ECP levels in serum.[14] However, one report described an exacerbation of symptoms and a rebound eosinophilia as drug levels waned.[13] Reinstitution of monthly anti–IL-5 treatment led to decreased eosinophilia and symptomatic improvement.[13] Here we describe a rebound eosinophilia in 10 of 16 patients with NP after anti–IL-5 treatment but without major exacerbation of symptoms. In the 3 mg/kg treatment group the rebound was less dramatic and later than in the 1 mg/kg group, suggesting that higher concentrations, repeated dosing, or both of anti–IL-5 mAbs might overcome rebound effects. Currently, none of the present studies in asthma, hypereosinophilic syndrome, or nasal polyps were large enough to detect different subgroups and to differentiate between patients with IL-5–dependent disease from those mainly dependent on other mediators. Long-term studies in well-characterized patients are therefore needed and should include analysis of local IL-5 and other cytokines or chemokines.

In summary, we here show that anti–IL-5 treatment results in a decrease in the volume of nasal polyps only in patients with increased nasal IL-5 levels. It is therefore suggested to select appropriate patients before conducting further clinical trials with IL-5 antagonists. Furthermore, a combination therapy with anti–IL-5 and a CCR3 antagonist might be another successful approach because this would have the advantage of inhibiting both bone marrow maturation (primarily IL-5 dependent) and tissue accumulation (mainly a CCR3-dependent effect).

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REFERENCES

1. Bachert C, Gevaert P, Holtappels G, Cuvelier C, van Cauwenberge P. Nasal polyposis: from cytokines to growth. Am J Rhinol 2000;14:279-90.
2. Settipane GA, Chafee FH. Nasal polyps in asthma and rhinitis. A review of 6,037 patients. J Allergy Clin Immunol 1977;59:17-21.
3. Denburg JA, Sehmi R, Upham J. Regulation of IL-5 receptor on eosinophil progenitors in allergic inflammation: role of retinoic acid. Int Arch Allergy Immunol 2001;124:246-8.
4. Sanderson CJ. Interleukin-5, eosinophils, and disease. Blood 1992;79:3101-9.
5. Bachert C, Wagenmann M, Hauser U, Rudack C. IL-5 synthesis is upregulated in human nasal polyp tissue. J Allergy Clin Immunol 1997;99:837-42.
6. Gevaert P, Bachert C, Holtappels G, Novo CP, Van der Heyden J, Fransen L, et al. Enhanced soluble interleukin-5 receptor alpha expression in nasal polyposis. Allergy 2003;58:371-9.
7. Simon HU, Yousefi S, Schranz C, Schapowal A, Bachert C, Blaser K. Direct demonstration of delayed eosinophil apoptosis as a mechanism causing tissue eosinophilia. J Immunol 1997;158:3902-8.
8. Greenfeder S, Umland SP, Cuss FM, Chapman RW, Egan RW. Th2 cytokines and asthma. The role of interleukin-5 in allergic eosinophilic disease. Respir Res 2001;2:71-9.
9. Flood-Page P, Menzies-Gow A, Phipps S, Ying S, Wangoo A, Ludwig MS, et al. Anti-IL-5 treatment reduces deposition of ECM proteins in the bronchial subepithelial basement membrane of mild atopic asthmatics. J Clin Invest 2003;112:1029-36.
10. Flood-Page PT, Menzies-Gow AN, Kay AB, Robinson DS. Eosinophil's role remains uncertain as anti-interleukin-5 only partially depletes numbers in asthmatic airway. Am J Respir Crit Care Med 2003;167:199-204.
11. Leckie MJ, ten Brinke A, Khan J, Diamant Z, O'Connor BJ, Walls CM, et al. Effects of an interleukin-5 blocking monoclonal antibody on eosinophils, airway hyper-responsiveness, and the late asthmatic response. Lancet 2000;356:2144-8.
12. Kips JC, O'Connor BJ, Langley SJ, Woodcock A, Kerstjens HA, Postma DS, et al. Effect of SCH55700, a humanized anti-human interleukin-5 antibody, in severe persistent asthma: a pilot study. Am J Respir Crit Care Med 2003;167:1655-9.
13. Klion AD, Law MA, Noel P, Haverty TP, Nutman TB. Safety and efficacy of the monoclonal anti-interleukin 5 antibody, SCH55700, in the treatment of patients with the hypereosinophilic syndrome. Blood 2004;103:2939-41.
14. Plotz SG, Simon HU, Darsow U, Simon D, Vassina E, Yousefi S, et al. Use of an anti-interleukin-5 antibody in the hypereosinophilic syndrome with eosinophilic dermatitis. N Engl J Med 2003;349:2334-9.
15. Liu LY, Sedgwick JB, Bates ME, Vrtis RF, Gern JE, Kita H, et al. Decreased expression of membrane IL-5 receptor alpha on human eosinophils: II. IL-5 down-modulates its receptor via a proteinase-mediated process. J Immunol 2002;169:6459-66.
16. Liu LY, Sedgwick JB, Bates ME, Vrtis RF, Gern JE, Kita H, et al. Decreased expression of membrane IL-5 receptor alpha on human eosinophils: I. Loss of membrane IL-5 Receptor alpha on airway eosinophils and increased soluble IL-5 receptor alpha in the airway after allergen challenge. J Immunol 2002;169:6452-8.
17. Foster PS, Hogan SP, Yang M, Mattes J, Young IG, Matthaei KI, et al. Interleukin-5 and eosinophils as therapeutic targets for asthma. Trends Mol Med 2002;8:162-7.
18. Foster PS, Hogan SP, Ramsay AJ, Matthaei KI, Young IG. Interleukin 5 deficiency abolishes eosinophilia, airways hyperreactivity, and lung damage in a mouse asthma model. J Exp Med 1996;183:195-201.
19. Mould AW, Ramsay AJ, Matthaei KI, Young IG, Rothenberg ME, Foster PS. The effect of IL-5 and eotaxin expression in the lung on

eosinophil trafficking and degranulation and the induction of bronchial hyperreactivity. J Immunol 2000;164:2142-50.
20. Tournoy KG, Kips JC, Schou C, Pauwels RA. Airway eosinophilia is not a requirement for allergen-induced airway hyperresponsiveness. Clin Exp Allergy 2000;30:79-85.
21. Tournoy KG, Kips JC, Pauwels RA. The allergen-induced airway hyperresponsiveness in a human-mouse chimera model of asthma is T cell and IL-4 and IL-5 dependent. J Immunol 2001;166:6982-91.
22. Gregory B, Kirchem A, Phipps S, Gevaert P, Pridgeon C, Rankin SM, et al. Differential regulation of human eosinophil IL-3, IL-5, and GM-CSF receptor alpha-chain expression by cytokines: IL-3, IL-5, and GM-CSF down-regulate IL-5 receptor alpha expression with loss of IL-5 responsiveness, but up-regulate IL-3 receptor alpha expression. J Immunol 2003;170:5359-66.
23. Murata Y, Takaki S, Migita M, Kikuchi Y, Tominaga A, Takatsu K. Molecular cloning and expression of the human interleukin 5 receptor. J Exp Med 1992;175:341-51.
24. Tavernier J, Tuypens T, Plaetinck G, Verhee A, Fiers W, Devos R. Molecular basis of the membrane-anchored and two soluble isoforms of the human interleukin 5 receptor alpha subunit. Proc Natl Acad Sci U S A 1992;89:7041-5.
25. Tavernier J, Tuypens T, Verhee A, Plaetinck G, Devos R, Van der Heyden J, et al. Identification of receptor-binding domains on human interleukin 5 and design of an interleukin 5-derived receptor antagonist. Proc Natl Acad Sci U S A 1995;92:5194-8.
26. Tuypens T, Plaetinck G, Baker E, Sutherland G, Brusselle G, Fiers W, et al. Organization and chromosomal localization of the human interleukin 5 receptor alpha-chain gene. Eur Cytokine Netw 1992;3:451-9.