



Letter

Efficacy of omalizumab in eosinophilic chronic rhinosinusitis patients with asthma

Introduction

Eosinophilic chronic rhinosinusitis (ECRS), a subtype of chronic rhinosinusitis with eosinophil-enriched nasal polyps, is an intractable comorbidity of severe asthma. Because elevated immunoglobulin E (IgE) levels, in particular against *Staphylococcus aureus* enterotoxin, are detected in nasal polyps of ECRS,¹ the anti-IgE antibody omalizumab was expected to improve ECRS, although its efficacy has been inconsistent.^{1,2} In this prospective, uncontrolled study, we evaluated the efficacy of omalizumab in ECRS patients with severe asthma. The primary endpoint was changes in Lund-Mackay sinus computed tomographic (CT) scores. Secondary outcomes were correlations between changes in measures for sinusitis and asthma after 16 weeks of treatment. The sample size was determined based on a previous study.² We also examined serum levels of periostin, an extracellular matrix protein that is induced by Th2 cytokines and is upregulated in asthma³ and ECRS.⁴

Six ECRS patients with severe atopic asthma (2 were sensitized to *Staphylococcus aureus* enterotoxin) were enrolled (Table 1) from July 2009 to November 2011. Two had concomitant eosinophilic otitis media (EOM), another intractable comorbidity of asthma. Asthma was diagnosed based on the criteria of the American Thoracic Society. ECRS⁵ and EOM were diagnosed based on diagnostic criteria. The study protocol (UMIN000002389) was approved by the Ethics Committee of each institute, and written informed consent was obtained from all participants.

Omalizumab was administered according to dosing tables. Participants were examined by pulmonologists and otolaryngologists, and they underwent the following examinations at baseline and at 16 weeks: a Sino-Nasal Outcome Test (SNOT-20),⁶ a questionnaire on nasal blockage and dysosmia, sinus CT graded using the Lund-Mackay system, Asthma Control Questionnaire, pulmonary function test, and sputum eosinophil count. Serum periostin levels were determined using an enzyme-linked immunosorbent assay.⁷ One patient could not undergo several tests because of time constraints. Two patients with EOM underwent pure tone audiometry and temporal bone CT.

JMP system version 6 (SAS Institute Japan, Tokyo, Japan) was used for statistical analysis. A paired *t*-test was used to compare pre- and post-treatment results. Relationships among variables were assessed using Pearson's correlation coefficients. The value $P \leq .05$ was considered statistically significant.

For 6 patients with ECRS, we observed significant improvements at 16 weeks in total and rhinological symptom scores of SNOT-20,

scores for nasal blockage ($P = .007$) and dysosmia ($P = .009$), and Asthma Control Questionnaire scores (Table 1). Sinus CT scores were also significantly reduced, particularly in the ethmoid sinus, the most susceptible region in ECRS (Table 1). The size of nasal polyps was reduced in 4 patients. In 1 patient with concomitant EOM (patient 3), perforation of the eardrum, the air conduction hearing level, and mastoiditis as evaluated by CT were improved.

At 16 weeks, changes in rhinological symptom scores of SNOT-20 were correlated with changes in sputum eosinophil counts ($r = 0.81$, $P = .05$; $n = 4$). Changes in sinus CT scores were correlated with changes in closing volume ($r = 0.92$, $P = .008$; $n = 6$), but were not correlated with changes in forced expiratory volume in 1 second ($r = -0.25$, $P = .63$) or maximally mid-expiratory flow ($r = -0.49$, $P = .33$) (data not shown). Furthermore, changes in ethmoid sinus CT scores were correlated with changes in serum periostin levels ($r = 0.89$, $P = .041$; $n = 5$). No other significant associations were found between ECRS outcome measures and lower airways measures.

This study demonstrated that omalizumab improved rhinological symptoms and sinus CT scores, and controlled asthma in ECRS patients with severe asthma. ECRS⁵ is refractory to conventional treatment and sometimes leads to anosmia. Although the mechanisms underlying the efficacy of omalizumab in ECRS remain unclear, omalizumab was effective for refractory ECRS in this study. Furthermore, changes in rhinological symptoms or sinus CT scores were correlated with changes in sputum eosinophil counts and serum periostin levels. These associations may suggest that omalizumab is concurrently effective for ECRS and severe atopic asthma, which share the similar histopathological features of eosinophilic/Th2 inflammation and airway remodeling. In particular, the association between changes in sinus CT scores and changes in closing volume, an index of ventilation heterogeneity that largely reflects small airway obstruction, may support a link between ECRS and severe asthma because small airway obstruction plays an important role in severe asthma.⁸ We cannot draw any definitive conclusions because the sample size of this study was small and the improvements in outcome measures were modest. However, these findings may provide a basis for future research on ECRS and severe asthma that can be referred to as a "severe unified airway disease."

In conclusion, omalizumab was concurrently effective for ECRS patients with severe asthma.

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Table 1
Baseline characteristics of ECRS patients with severe asthma

Pt.	Age, Years	Sex	IgE IU/mL	EOM	SNOT-20 Scores				Lund-Mackay CT Scores				ACQ Scores	
					Total		Rhinological		Total		Ethmoid Sinus		Total	
					Base	16 wk	Base	16 wk	Base	16 wk	Base	16 wk	Base	16 wk
1	51	F	320	Y	35	20	9	1	10	5	4	2	0.43	0.29
2	78	M	300	N	37	21	13	5	12	11	4	4	2.29	0.14
3	67	M	560	Y	56	47	11	12	8	6	4	2	1.86	0.86
4	55	F	102	N	10	3	6	2	24	20	8	8	1.14	0.43
5	51	F	120	N	38	30	11	5	7	2	4	2	0.57	0.29
6	55	M	590	N	42	18	9	5	19	12	8	5	3.14	0.86
Mean (SD)	60 (11)	—	332 (209)	—	36 (15)	23 (15)	10 (2)	5 (4)	13.3 (6.7)	9.3 (6.4)	5.3 (2.1)	3.8 (2.4)	1.6 (1.1)	0.5 (0.3)
P value^a	—	—	—	—	.005		.017		.007		.030		.034	

EOM, eosinophilic otitis media; F, female; M, male; Y, yes; N, no; SNOT-20, Sino-Nasal Outcome Test 20; ACQ, Asthma Control Questionnaire; base, baseline; 16 wk, 16 weeks.

^aBy paired *t*-test.

Tomoko Tajiri, MD*
 Hisako Matsumoto, MD, PhD*
 Harukazu Hiraumi, MD, PhD†
 Hiroki Ikeda, MD, PhD‡
 Kyohei Morita, MD§
 Kenji Izuhara, MD, PhD||
 Junya Ono, BS¶
 Shoichiro Ohta, MD, PhD#
 Isao Ito, MD, PhD*
 Tsuyoshi Oguma, MD*
 Hitoshi Nakaji, MD*,§
 Hideki Inoue, MD*
 Toshiyuki Iwata, MD*
 Tadao Nagasaki, MD*
 Yoshihiro Kanemitsu, MD*
 Juichi Ito, MD, PhD†
 Akio Niimi, MD, PhD*,**
 Michiaki Mishima, MD, PhD*

*Department of Respiratory Medicine
 Graduate School of Medicine
 Kyoto University
 Kyoto, Japan

†Department of Otolaryngology
 Graduate School of Medicine
 Kyoto University
 Kyoto, Japan

‡Department of Otolaryngology
 Japanese Red Cross Wakayama Medical Center
 Wakayama, Japan

§Department of Respiratory Medicine
 Japanese Red Cross Wakayama Medical Center
 Wakayama, Japan

||Division of Medical Biochemistry
 Department of Biomolecular Sciences

Saga Medical School
 Saga, Japan

¶Shino-Test Science Corporation
 Kanagawa, Japan

#Department of Laboratory Medicine
 Saga Medical School
 Saga, Japan

**Division of Respiratory Medicine
 Department of Medical Oncology and Immunology
 Nagoya City University School of Medical Sciences
 Aichi, Japan

hmatsumo@kuhp.kyoto-u.ac.jp

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