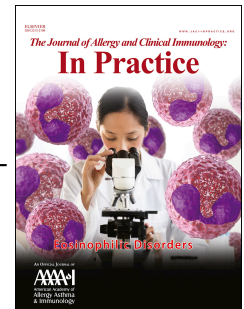


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Add-on omalizumab for inadequately controlled severe pollinosis despite standard-of-care: a randomized study

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Title

Add-on omalizumab for inadequately controlled severe pollinosis despite standard-of-care: a randomized study

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Conflict of interest:

K. Okubo reports being a medical advisor of the study and receiving personal fees from Novartis Pharma during the conduct of the study; personal fees from Torii Pharmaceutical, Taiho Pharmaceutical, Mitsubishi-Tanabe Pharma, Meiji Seika Pharma, Kyorin Pharmaceutical, Ceolia Pharma, and Astellas Pharma outside the submitted work. M. Okano reports being a medical advisor of the study and receiving personal fees from Novartis Pharma during the conduct of the study; personal fees from Kyorin Pharm Co. and Sanofi; and grants and personal fees from Tanabe Mitsubishi Pharm and Taiho Pharm Co. outside the submitted work. N. Sato, Y. Tamaki, H. Suzuki, A. Uddin and R. Fogel report being employees of Novartis Pharma.

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ABSTRACT**Background**

Cedar pollinosis (CP), a common form of seasonal allergic rhinitis (AR), is a substantial medical problem in Japan due to its high prevalence and severe symptoms. Omalizumab (anti-IgE therapy) has previously proven effective in CP/AR, but no studies for inadequately controlled severe CP/AR despite standard-of-care (SoC) have been conducted.

Objective

To determine the efficacy of omalizumab added to SoC in patients with inadequately controlled severe CP in a randomized, double-blinded, placebo-controlled, phase III study.

Methods

Severe adult/adolescent CP patients whose symptoms were inadequately controlled despite nasal corticosteroids plus one or more oral medications in the previous two seasons were randomized to receive omalizumab (n = 162) or placebo (n = 175). All patients received concomitant antihistamines and nasal corticosteroids as SoC. The primary endpoint was the mean nasal symptom score during the severe symptom period. Secondary endpoints included mean ocular symptom score, quality-of-life, and safety.

Results

The SoC + omalizumab treatment had statistically significantly and clinically important lower nasal (LS mean difference, -1.03, $p < 0.001$) and ocular (-0.87, $p < 0.001$) symptom scores compared with SoC + placebo respectively. Differences in scores for individual components of nasal and ocular symptoms were also statistically and clinically significant. SoC + Omalizumab also improved QoL scores as overall and in all domains. No unexpected safety signals were observed.

Conclusions

In severe CP patients, omalizumab added to SoC demonstrated consistent efficacy in improving symptoms and QoL, and was well-tolerated. These results indicate omalizumab could be a promising therapeutic option for severe CP/AR.

(246/250 words)

The clinical trial registration number: ClinicalTrials.gov: NCT03369704; EudraCT: 2017-002154-36

Highlights Box

What is already known about this topic?

Omalizumab (anti-IgE therapy) has previously proven effective in allergic rhinitis (AR) including cedar pollinosis (CP), but the effect of add-on omalizumab for inadequately controlled severe CP/AR despite standard-of-care (SoC) is unknown.

(31/35 words)

What does this article add to our Knowledge?

Our randomized, placebo-controlled, phase III study provides the first evidence that in inadequately controlled severe CP patients despite SoC, add-on omalizumab led to consistent efficacy in improving symptoms, quality-of-life, work productivity and was well-tolerated.

(34/35 words)

How does this study impact current management guidelines?

Our study results indicate that omalizumab could be a new promising treatment option for patients with inadequately controlled severe CP/AR and optimize the overall management of these patients.

(28/35 words)

97

98 **Keywords:** antihistamines, allergic rhinitis, nasal corticosteroids, nasal symptom, ocular
99 symptom, omalizumab, quality of life, work productivity, severe cedar pollinosis

100

101 **Abbreviations:**

102 AEs: Adverse events

103 AR: Allergic rhinitis

104 ARIA: Allergic Rhinitis and its Impact on Asthma

105 CI: Confidence interval

106 CP: Cedar pollinosis

107 FAS: Full analysis set

108 IgE: Immunoglobulin E

109 JRQLQ: Japanese Rhino-conjunctivitis Quality of Life Questionnaire

110 LS mean: Least squares mean

111 LTRA: Leukotriene receptor antagonist

112 QoL: Quality-of-life

113 SAEs: Serious AEs

114 SoC: Standard-of-care

115 WPAI-AS: Work Productivity and Activity Impairment Questionnaire-Allergy Specific

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INTRODUCTION

Allergic rhinitis (AR) is one of the most common and increasingly prevalent diseases worldwide, affecting over 500 million people.^{1,2} Major symptoms of AR are sneezing, watery rhinorrhea, nasal congestion and nasal itching, frequently accompanied by ocular symptoms including itchy and watery eyes. AR greatly reduces quality-of-life (QoL), impairing daily activities including work/school performance, and sleep quality.¹⁻⁴

In Japan, cedar pollinosis (CP), a form of seasonal AR caused by Japanese cedar pollen (*Cryptomeria japonica*), is a substantial medical problem due to its high prevalence and severe symptoms.^{2,5} Approximately 30% of the Japanese population suffered from CP in 2008, which was a 10% increase compared with 1998.² In addition, a recent survey conducted by the Tokyo Metropolis showed that the prevalence of this disorder in Tokyo in 2017 has been estimated to be 45.6%.⁶ Japanese cedar trees, covering approximately 18% of the total land area of Japan produce large amounts of pollen, which can travel long distances (>100 km in some cases), thus reaching big cities including Tokyo and Osaka.^{5,7} In Tokyo, the pollen season starts in early/mid-February and lasts until mid/late-April; between early March and early April, the pollen scatters heavily. The subsequent exposure is the cause of severe symptoms of CP. An internet-based survey reported that more than 90% of CP patients were moderate/severe on the symptom scale according to the Allergic Rhinitis and its Impact on Asthma (ARIA) guideline.⁸

Oral antihistamines and nasal corticosteroids are the primary treatments for AR including CP.^{1,2,9} The Japanese guideline for AR² recommends early intervention just after the development of symptoms or the start of pollen dispersal. Oral antihistamines are most frequently used for the initial treatment. Nasal corticosteroids are generally added for subsequent aggravation of nasal symptoms along with the increasing amount of pollen scattered as the season progresses. Leukotriene receptor antagonists (LTRAs) or vasoconstrictor agents are available for patients with severe nasal congestion. According to an

internet survey,⁸ approximately 50% of Japanese patients had severe symptoms in the CP season based on the Japanese guideline,² and 10% were unsatisfied with the efficacy of current standard-of-care (SoC). Severe CP symptoms impair patients' QoL, making the disease a huge burden for the patients.^{2,5,8,10} Of note, the market for CP medications and the economic cost due to absenteeism in CP is estimated to be approximately 200 to 300 billion yen (2.2-3.3 billion US dollars) and 60 billion yen (543 million US dollars) per season, respectively.⁵

Consequently, new treatments are needed for those patients whose symptoms are inadequately controlled with SoC. The recommended treatment strategy for AR from the ARIA guideline¹ is to combine interventions at different levels, which should improve the clinical outcome; thus, a medication with a different mode of action from the current SoC would be expected to be most efficacious.

Omalizumab is a humanized anti-immunoglobulin E (IgE) antibody, which blocks the binding of IgE to high-affinity receptors (FcεRI) on effector cells including mast cells and basophils,¹¹ thereby preventing the activation of the IgE-mediated allergic cascade.¹² Omalizumab is indicated for treatment of moderate-to-severe allergic asthma and chronic spontaneous/idiopathic urticaria worldwide.¹³ AR including CP is a type I allergic disease mediated by allergen-specific IgE, therefore omalizumab is expected to be effective for these diseases.

In fact, previous studies demonstrated that omalizumab was effective and safe in patients with AR induced by various kinds of allergens, such as ragweed,^{14,15} birch pollen^{16,17} and dust mite;¹⁸ In Japan, CP compared with placebo¹⁹ and suplatast tosilate (a selective T-helper type 2 cytokine inhibitor),²⁰ and in treatment for two consecutive CP seasons.²¹ However, no studies to date have evaluated the effect of add-on omalizumab in patients with inadequately controlled severe CP/AR despite SoC. This randomized, double-blinded phase III study was designed to demonstrate the efficacy and safety of omalizumab compared with placebo, as an add-on to

SoC (antihistamines and nasal corticosteroids) in adult and adolescent patients with inadequately controlled severe CP during the previous two seasons.

METHODS

Study design

This randomized, double-blind, parallel-group, placebo-controlled phase III study was conducted at 22 sites in and around Tokyo in Japan between December 2017 and October 2018 (ClinicalTrials.gov: NCT03369704; EudraCT: 2017-002154-36). The study consisted of 3 distinct study periods: a screening period (1 to 5 weeks), a double-blind treatment period (12 weeks), and a post-treatment follow-up (24 weeks after the last dose of study drug; Fig 1). Following screening, eligible patients were assigned (1:1) to omalizumab or placebo group added to SoC via interactive response technology using stratified block randomization (randomization strata: age group, coexistence of perennial AR, dose frequency and presence of symptom at initial drug administration). As SoC, all patients received concomitant antihistamines and nasal corticosteroids; Fexofenadine hydrochloride (oral, 120 mg/day, twice daily) was used throughout the treatment period. For 4 weeks (March 5 to April 1) which was expected to be the severe pollen scattering season, nasal fluticasone propionate (100 µg/day, twice daily for aged ≥ 12 to < 15 years; 200 µg/day, twice daily for aged ≥ 15 to < 75 years) was used, irrespective of their symptoms. Permitted rescue medication during the treatment period, included tramazoline hydrochloride (0.118% nasal solution) and levocabastine hydrochloride (0.025% ophthalmic solution). An electronic diary was used to record nasal/ocular symptoms, and usage of rescue medications on a daily basis. At the post treatment follow-up, blood was collected for assessments of anti-omalizumab antibody.

The study protocol was approved by the Institutional Review Board at each site. All patients provided written informed consent.

Patients

Eligible patients were aged ≥12 to <75 years with confirmed diagnosis of inadequately controlled severe CP despite nasal corticosteroids plus one or more oral medications from

(i) antihistamine, (ii) LTRA, or (iii) prostaglandin D₂/thromboxane A₂ receptor antagonist in the previous two seasons, and with levels of serum specific IgE to cedar pollen (ImmunoCAP) of ≥ 3.5 UA/mL (class 3). Patients must have had inadequately controlled symptoms lasting at least 1 week defined as presence of all symptoms including sneezing, rhinorrhea, and nasal congestion, which were in total categorized as most severe or severe according to the Japanese guideline (see Table E1,A and B in the online repository).² Key exclusion criteria were patients with active rhinitis other than AR (e.g., acute or chronic rhinitis, or idiopathic rhinitis), an active nose disease other than AR (e.g., acute or chronic rhinosinusitis, or deviated septum) which could affect the evaluation of efficacy, elevated serum IgE levels for reasons other than allergy, and operative treatment for AR within 1 year prior to the study.

Doses and administration

Dose (75 to 600 mg) and dosing frequency (every 2 or 4 weeks) of omalizumab or matching placebo by subcutaneous injection were determined by serum total IgE level (IU/mL) and body weight (kg) measured during the screening period, according to the same dosing table (see Table E2 in the online repository) as that for allergic asthma.²² This dosing table was used in the majority of previous omalizumab studies for AR including CP.¹⁸⁻²¹ Initial administration of study drug was planned from January 19 to February 10.

Endpoints and assessments

The primary endpoint was the mean nasal symptom score with omalizumab versus placebo during the severe symptom period. The nasal symptom score (0–12 points) consists of the sum of the scores of severity of sneezing (0–4 points), rhinorrhea (0–4 points), and nasal congestion (0–4 points, where 0 is none and 4 is severe) according to the Japanese guideline (see Table E1,A in the online repository).² The severe symptom period was defined as the consecutive 3 weeks where the cumulative value of the mean daily nasal symptom score was the maximum.²³

The mean daily nasal symptom score was defined as the total nasal symptom score of all patients, divided by the non-missing number of patients per day. The 3 weeks must have met one of the following criteria: (i) $\geq 70\%$ of the period with concomitant use of fluticasone propionate was included in this 3 weeks or (ii) $\geq 70\%$ of this 3 weeks included the period with concomitant use of fluticasone propionate and if (i) or (ii) were not met then, severe symptom period was to be extended at a minimum to meet one of them.

Secondary endpoints included mean ocular symptom score, nasal and ocular rescue medication scores, nasal symptom free days, Japanese Rhino-conjunctivitis Quality of Life Questionnaire (JRQLQ No.1 part II) score^{2,24-26} and safety. Ocular symptom score (0–8 points) is the sum of the scores for severity of itchy eye (0–4 points) and watery eye (0–4 points) (see Table E3 in the online repository). Rescue medication scores were given for tramazoline hydrochloride (1 point), and levocabastine hydrochloride (1 point).² Severity in nasal symptom was subdivided into 5 categories (most severe, severe, moderate, mild and no symptom) according to the Japanese guideline (see Table E1,B in the online repository)² and a nasal symptom free day was defined as a day where all nasal symptoms were not more than mild in severity. The JRQLQ includes 17 QoL-related questionnaire (0-4 points), which were divided into 6 domains including; usual daily activities, outdoor activities, social functioning, sleep problem, general physical problems, and emotional function.²⁴ Safety was assessed by monitoring adverse events (AEs) during the treatment period. Anti-omalizumab antibodies (IgG) were measured by ELISA as previously described.¹⁴

Exploratory endpoints included Work Productivity and Activity Impairment Questionnaire-Allergy Specific (WPAI-AS) score.^{10,27}

Statistical analysis

A sample size of 155 patients per group was required to provide 90% power to detect a 0.87 difference in the mean nasal symptom score between treatment groups, assuming a

significance level of 0.05 (two-sided) and a common standard deviation of 2.35. A 0.87 difference (0.29 for each nasal symptom of sneezing, rhinorrhea and nasal congestion) was considered clinically relevant.²⁸ Assuming an early discontinuation rate of approximately 10%, a total of 346 patients were planned to be randomized.

Statistical analyses of efficacy variables were performed on the full analysis set (FAS), which consisted of all randomized patients who received at least one dose of the study drug. Following the intent-to-treat principle, patients in the FAS were analyzed according to the treatment assigned at randomization. Among patients in the FAS, those who recorded their nasal symptom scores on at least 50% of days during the severe symptom period were included in the analyses for symptom and medication scores. For primary analysis, the mean nasal symptom score was compared between treatments using an analysis of variance model with treatment group, and randomization strata. Least squares (LS) means difference between treatment groups and corresponding 95% confidence interval (CI) as well as p-value were calculated based on the model, considering a weight of the strata. The statistical analysis tested the null hypotheses of no difference between omalizumab and placebo at the 2-sided significance level of 5%. In addition, subgroup analyses by baseline characteristics were performed. The secondary efficacy variables (mean symptom score, and mean rescue medication score) were analyzed using the same model as the primary variable. The JRQLQ score and the WPAI-AS score at the severe symptom period was analyzed using the same model as the primary efficacy variable. The number of nasal symptom free days during the severe symptom period was analyzed by stratified Wilcoxon rank sum (van Elteren) test with randomization strata. Stratified Hodges-Lehmann estimate for the median was derived for the difference between treatment groups with its CI and p-value from van Elteren test. Descriptive statistics were used to summarize number of days with each nasal symptom severity during the severe symptom period and all safety variables. The assessment of safety was performed on all patients who

received at least one dose of study drug. Patients were grouped according to treatment they

received. Missing data were not imputed.

SAS version 9.4 (SAS Institute Inc, Cary, NC) was used for all analyses.

RESULTS

Patients

Of 337 randomized patients, 336 patients [omalizumab group added to SoC (SoC + omalizumab), n = 161; placebo group added to SoC (SoC + placebo), n = 175] received injections of the study drug on Day 1, and 330 patients (97.9%) completed the treatment period (Fig 2). In both treatment groups, approximately 90% of the patients received study drug 4-weekly.

The baseline demographics and clinical characteristics were well balanced between the treatment groups. The mean duration of CP was more than 15 years. Approximately 50% of the patients had comorbid Japanese cypress (*Chamaecyparis obtusa*) pollinosis and 35% had perennial AR. In the previous season, almost all the patients were treated with nasal corticosteroids and antihistamines, but approximately 60% had most severe and 40% had severe nasal symptoms, respectively (Table I).

Time course of nasal and ocular symptom scores

Throughout the severe symptom period (February 23 to March 24), daily mean nasal and ocular symptom score with the SoC + omalizumab treatment were lower versus SoC + placebo (Fig 3,A and B).

Nasal symptom score

The study met its primary endpoint of mean nasal symptom score during the severe symptom period, demonstrating statistically significant ($p < 0.001$) reduction with SoC + omalizumab versus SoC + placebo (Fig 4,A). The difference between treatment groups (1.03) exceeded the pre-specified clinically relevant difference of 0.87.²⁸ Scores for all individual symptoms

(sneezing, rhinorrhea, and nasal congestion) were consistently lower with SoC + omalizumab than with SoC + placebo (Fig 4,B).

A post-hoc analysis similar to the primary analysis examined the mean nasal symptom score during the severe symptom period that overlapped with the period of concomitant use of nasal corticosteroids (March 5 to 24) showed significant differences between treatment groups [LS mean, 3.40 (SoC + omalizumab) vs 4.24 (SoC + placebo); the difference (95% CI), -0.85 (-12.9,-0.40); $p < 0.001$].

Total percentage of days for most severe and severe symptoms during the severe symptom period were lower with SoC + omalizumab than with SoC + placebo (most severe, 2.4% days vs 12.3% days; severe, 10.5% days vs 17.4% days; Fig 4,C). The median number of nasal symptom free days was also greater in the SoC + omalizumab group (15.0) than in the SoC + placebo group (10.0). The stratified Hodges-Lehmann estimate (95% CI) for the median difference between the treatment groups was 3.0 (1.0, 5.0), with p -value of 0.005.

Nasal symptom scores - subgroup analyses

The results of subgroup analyses by baseline characteristics (age, gender, coexistence of perennial AR, severity of nasal symptom in the previous season, total IgE levels and cedar pollen-specific IgE levels) on the primary endpoint were consistent with those of the overall study population for all subgroups (see Fig E1 in the online repository).

Ocular symptom score

SoC + omalizumab significantly reduced the ocular symptom score compared with SoC + placebo ($p < 0.001$) during the severe symptom period (Fig 5,A). Scores for the individual two symptoms (itchy eye, watery eye) were consistently lower with SoC + omalizumab than with SoC + placebo (Fig 5,B).

Rescue medication use

SoC + omalizumab decreased both the mean nasal and ocular rescue medication score during the severe symptom period compared with SoC + placebo, respectively [LS mean (SE), 0.20 (0.024) vs 0.28 (0.023) for nasal; 0.46 (0.029) vs 0.54 (0.027) for ocular].

QoL and work productivity

The mean overall score of JRQLQ at the severe symptom period was lower with SoC + omalizumab than with SoC + placebo (difference in LS mean [95% CI], -0.51 [-0.69, -0.33]), which exceeded the minimal clinically important difference of 0.5.²⁸ The scores of all 6 domains (usual daily activities, outdoor activities, social functioning, sleep problem, general physical problem, emotional function) were significantly lower with SoC + omalizumab (Fig 6,A).

The mean WPAI-AS scores in the SoC + omalizumab group were lower than those in the SoC + placebo group for all domains (work time missed, impairment while working, overall work impairment and activity impairment; Fig 6,B).

Safety

Omalizumab was well tolerated with a safety profile that was similar between the treatment groups (Table II). The most frequently reported AEs ($\geq 2\%$ in either group) included nasopharyngitis, pharyngitis, and influenza. One SAE of testicular neoplasm was reported in the SoC + omalizumab group, which led to study drug discontinuation; it was resolved with surgery and was not considered related to the study drug. One additional patient in the SoC + omalizumab group discontinued study drug due to acute sinusitis and otitis media, which were resolving and not resolved, respectively, at the time of last observation. Neither event was suspected to be related to the study drug by the investigator. No positive post-dose anti-omalizumab antibodies were detected.

DISCUSSION

To the best of our knowledge, this is the first study to demonstrate that omalizumab added to SoC (nasal corticosteroids and antihistamines) is clinically effective and well-tolerated in patients with inadequately controlled severe CP despite current recommended therapies. In Japan, approximately 50% of CP patients have severe symptoms during the season,⁸ suggesting a clear need for new treatments. Therefore, the study provides robust evidence that omalizumab represents a new promising treatment for severe CP as well as severe AR worldwide. In fact, based on the results of this study, omalizumab was approved for inadequately controlled severe seasonal AR despite SoC in December 2019 in Japan. In this study, omalizumab on top of SoC showed consistent efficacy in improving nasal and ocular symptoms, QoL and work productivity. SoC + omalizumab demonstrated a clinically significant improvement in mean nasal symptom score during the severe symptom period compared with SoC + placebo. The difference between treatment groups (1.03) exceeded the minimum clinical important difference of 0.87, established by Higaki et al.²⁸ This improvement was also supported by the results that patients treated with SoC + omalizumab had more nasal symptom-free days and fewer days with severe or most severe nasal symptoms. Furthermore, the post-hoc analysis showed significant benefits of omalizumab on nasal symptoms even in the period limited to use of concomitant nasal corticosteroids. In addition to nasal symptom score, ocular symptom score and individual nasal and ocular symptom scores were also improved with SoC + omalizumab, which indicate one of the advantages of omalizumab because both nasal and ocular symptoms of CP are associated with significant impairment in QoL including mental and physical functioning, and work performance.² In fact, SoC + omalizumab significantly improved all domains of JRQLQ, work productivity loss and activity impairment based on WPAI-AS. These improvements would support the role of omalizumab in the management of severe CP/AR.

As shown in Fig 3, nasal fluticasone was effective in preventing nasal symptoms in that daily mean nasal symptom scores in both treatment groups didn't substantially increase further at the time of the peak amount of cedar pollen scattering around 14th March, in contrast with daily mean ocular symptom scores. However, even after treatment with nasal fluticasone, daily mean nasal symptom score with SoC + omalizumab was consistently lower than that with SoC + placebo. As most anti-allergy drugs for AR including antihistamines²⁹⁻³¹ and LTRA^{31,32} have failed to show significant additive effects when used in combination with nasal corticosteroids, these results have important clinical implications. While the medications listed above only inhibit one type of mediator released from effector cells, omalizumab may have broader effects. It not only blocks upstream of the allergic cascade by inhibiting the binding of IgE to FcεRI but also downregulates the expression of FcεRI on inflammatory cells by reducing circulating free IgE.³³⁻³⁶ These mechanisms may contribute to the efficacy of omalizumab even in patients inadequately controlled with nasal corticosteroids. Similar add-on effects of omalizumab were observed in patients with severe allergic asthma inadequately controlled with inhaled corticosteroid plus other controller, such as long-acting β-agonist or LTRA.³⁷⁻³⁹ Therefore, a treatment strategy of combination with omalizumab and corticosteroid (and/or other anti-allergic drugs) is effective in several allergic disorders.

Previous studies have reported the noticeable effect of omalizumab for AR including CP, irrespective of allergen type.¹⁴⁻²¹ However, in these studies, SoC including nasal corticosteroids were not allowed as concomitant medication and comprehensive assessment for efficacy including nasal symptoms, QoL and work productivity were not conducted. Thus, this study adds to the growing body of evidence of the efficacy of omalizumab in patients with severe AR/CP.

Omalizumab requires some lead time to demonstrate optimal efficacy^{33,34} because omalizumab cannot bind to or inhibit the function of IgE already bound to FcεRI on the cell surface of mast cells or basophils. In this study, the initial administration of study drug was given on or before

February 10, just around the starting date of the pollen period, in order to ensure approximately 3–4 weeks before the start of the severe pollen period. This timing of initial drug administration was approximately one month later compared with our previous studies¹⁹⁻²¹ where the initial dose was typically administered in mid-January. The ability to begin omalizumab administration later and still demonstrate significant efficacy should be associated with decreased cost and patient burden.

Safety results from this study did not suggest any new or unexpected safety concerns and were consistent with the known safety profile of omalizumab.^{13,40} Therefore, omalizumab on top of SoC had a favorable benefit-risk profile.

The limitations of the current study or questions requiring further investigation should be recognized. First, in this study, concomitant nasal corticosteroids and antihistamines was fixed in both treatment groups to fairly evaluate the effect of omalizumab, whereas this could be flexible in real-life circumstances. Therefore, whether it is possible to reduce the need for SoC with the use of omalizumab while controlling symptoms would be an important question to address. In addition, the effect of combination treatment with omalizumab and subcutaneous/sublingual immunotherapy would be of high interest as omalizumab demonstrated additional clinical benefit when used in combination with subcutaneous immunotherapy in several preliminary studies of seasonal AR.^{17,41} Second, though omalizumab showed significant additive effect on SoC and controlled symptoms, it did not completely eliminate symptoms. One possible reason for refractory symptoms could be those that are parasympathetic nerve dominant or symptoms owing to a completely localized allergic response in the nasal mucosa (local AR).⁴² Therefore, further investigation including endotypes that respond adequately (or poorly) to omalizumab would be needed. Third, in this study, omalizumab has shown to improve QoL and work productivity as well as nasal and ocular symptoms, but cost-effectiveness of omalizumab would be unclear. Given the cost of omalizumab, a study/analysis to evaluate the cost-effectiveness of omalizumab should be

conducted, as has previously been performed in allergic asthma⁴³⁻⁴⁵ and spontaneous/idiopathic urticaria.⁴⁶ As a cost-effective analysis model appropriately adapted for cedar pollinosis/AR in Japan has not yet been developed, further research in terms of pharmacoeconomic perspective should strongly be desired in order to determine the most appropriate patients for this therapy. In conclusion, in patients with severe CP, omalizumab added to SoC consistently improved nasal and ocular symptoms, QoL and work productivity and was well-tolerated. Findings from this study indicate that omalizumab has potential to optimize the overall management of patients with severe CP/AR.

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Figure legends

FIG 1. Study design

FIG 1 footnote: SoC, standard of care: Fexofenadine (oral) and fluticasone (nasal); [†]Rescue medication: Fexofenadine (oral), tramazoline (nasal), and levocabastine (ocular); [‡]Period with concomitant fluticasone (nasal): March 5 to April 1

FIG 2. Patient disposition

FIG 2 footnote. SoC, standard of care: Fexofenadine (oral) and fluticasone (nasal)

FIG 3. Time course of daily mean nasal (A) and ocular (B) symptom scores by treatment (FAS)

FIG 3 footnote. SoC, standard of care: Fexofenadine (oral) and fluticasone (nasal); [†]Period with concomitant fluticasone (nasal): March 5 to April 1; [‡]The Severe symptom period (defined in the “Endpoint and assessments” section): February 23 to March 24; *Statistically significant differences ($p < 0.001$) between treatments were observed for both mean nasal symptom score and mean ocular symptom score during the severe symptom period (Detailed results are shown in Fig 4,A and Fig 5,A, respectively); [§]Cedar Pollen count measured with Durham method in Tokyo (Chiyoda ward), which was provided as a public service from Tokyo Metropolis. A total of 5023 grains/cm² cedar pollen were scattered in Tokyo in 2018 season.

FIG 4. Mean nasal symptom score (A) and individual nasal symptom scores (B) with SoC + omalizumab versus SoC + placebo during the severe symptom period (FAS); the difference (95% CI). *Statistically significant differences ($p < 0.001$). (C) Percentage of days with each nasal symptom severity during the severe symptom period by treatment.

FIG 4 footnote. SoC, standard of care: Fexofenadine (oral) and fluticasone (nasal)

FIG 5. Mean ocular symptom score (A) and individual symptom scores (B) with SoC + omalizumab versus SoC + placebo during the severe symptom period (FAS); the difference (95% CI). *Statistically significant differences ($p < 0.001$).

FIG 5 footnote. SoC, standard of care: Fexofenadine (oral) and fluticasone (nasal)

FIG 6. (A) Japanese rhinoconjunctivitis Quality of Life questionnaire score (FAS) (B) Work Productivity and Activity Impairment Questionnaire-Allergy Specific (WPAI-AS) score at the severe symptom period (FAS); the difference (95% CI). *Statistically significant differences ($p < 0.001$).

FIG 6 footnote. SoC, standard of care: Fexofenadine (oral) and fluticasone (nasal)

TABLE I. Baseline demographics and clinical characteristics (randomized population)

Characteristics	SoC + omalizumab (n = 162)	SoC + placebo (n = 175)
Age (years), median (range)	44.0 (12.0, 70.0)	42.0 (12.0, 74.0)
Gender		
Male	63 (38.9)	78 (44.6)
Female	99 (61.1)	97 (55.4)
Duration of CP (years), mean (SD)	18.2 (11.11)	15.4 (10.88)
CP related medical history (coexisting)		
Japanese cypress pollinosis [†]	84 (51.9)	77 (44.0)
Perennial AR	56 (34.6)	61 (34.9)
Asthma	6 (3.7)	6 (3.4)
Severity of nasal symptom in the previous season		
Most severe	91 (56.2)	102 (58.3)
Severe	71 (43.8)	72 (41.1)
Moderate	0	1 (0.6)
Medication use for CP in the previous season		
Nasal corticosteroid	162 (100)	174 (99.4)
Oral antihistamine	160 (98.8)	173 (98.9)
Leukotriene receptor antagonist	32 (19.8)	47 (26.9)
Prostaglandin D ₂ /thromboxane A ₂ receptor antagonist	0	1 (0.6)
Serum total IgE (IU/mL), mean (SD)	219.9 (223.48)	227.6 (238.85)
Class of cedar pollen-specific IgE		
6 [≥100 (UA/mL)]	4 (2.5)	6 (3.4)
5 [≥50, < 100 (UA/mL)]	13 (8.0)	17 (9.7)
4 [≥17.5, < 50 (UA/mL)]	53 (32.7)	50 (28.6)
3 [≥3.5, < 17.5 (UA/mL)]	92 (56.8)	102 (58.3)

SoC, standard of care: Fexofenadine (oral) and fluticasone (nasal)

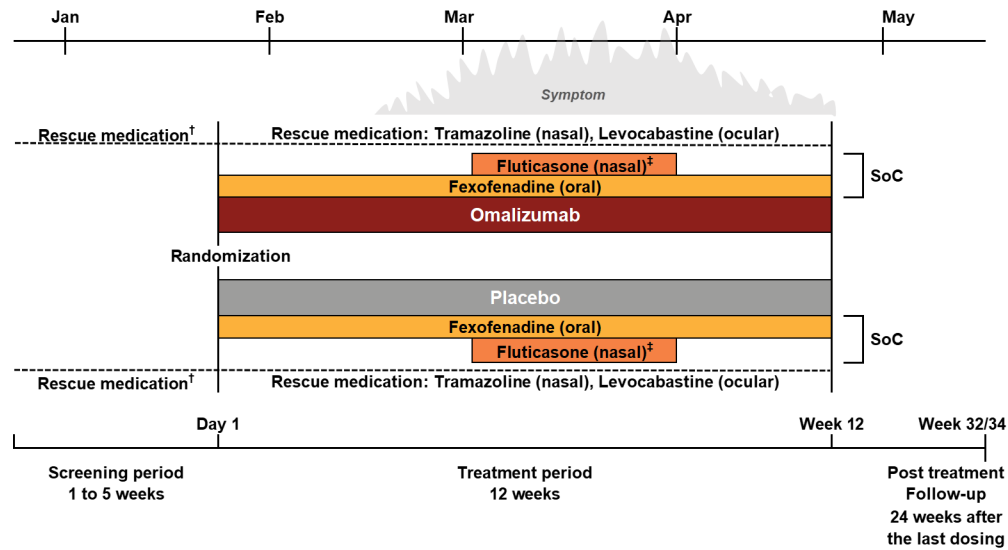
Data are presented as n (%), unless otherwise indicated.

[†]Japanese cypress pollinosis usually develops in April, following the CP season.**TABLE II.** Summary of treatment emergent AEs

	SoC + omalizumab (n = 161)	SoC + placebo (n = 175)
Death	0	0
SAEs	1 (0.6)	0
AEs leading to discontinuation	2 (1.2)	0
Any AEs	44 (27.3)	48 (27.4)
Most frequently occurring AEs (≥2% in either group)		
Nasopharyngitis	15 (9.3)	8 (4.6)
Pharyngitis	7 (4.3)	5 (2.9)
Influenza	4 (2.5)	8 (4.6)

SoC, standard of care: Fexofenadine (oral) and fluticasone (nasal)

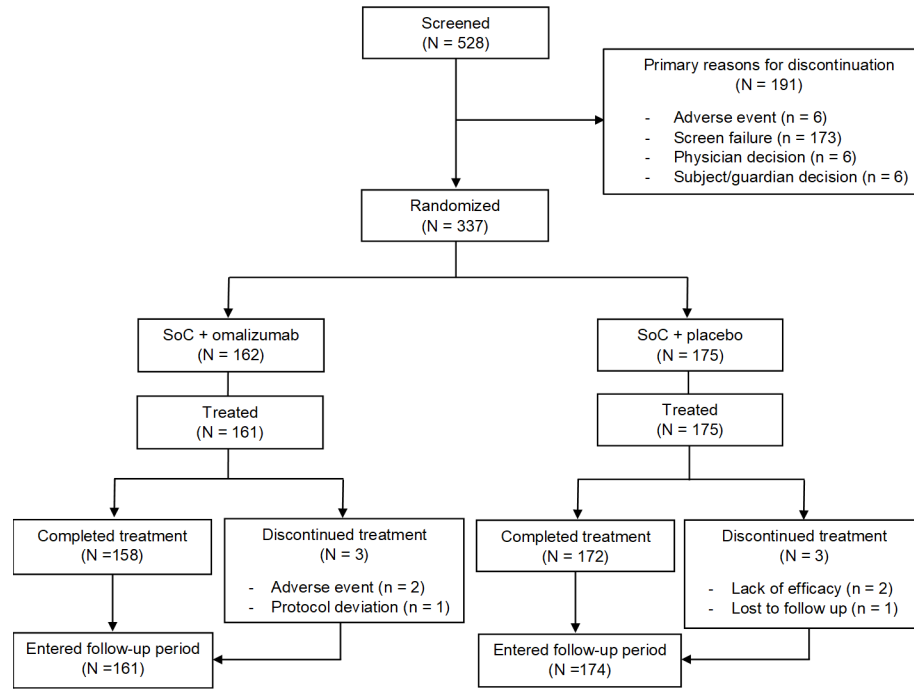
Data are presented as n (%), unless otherwise indicated. AE, adverse event; SAE, serious adverse event

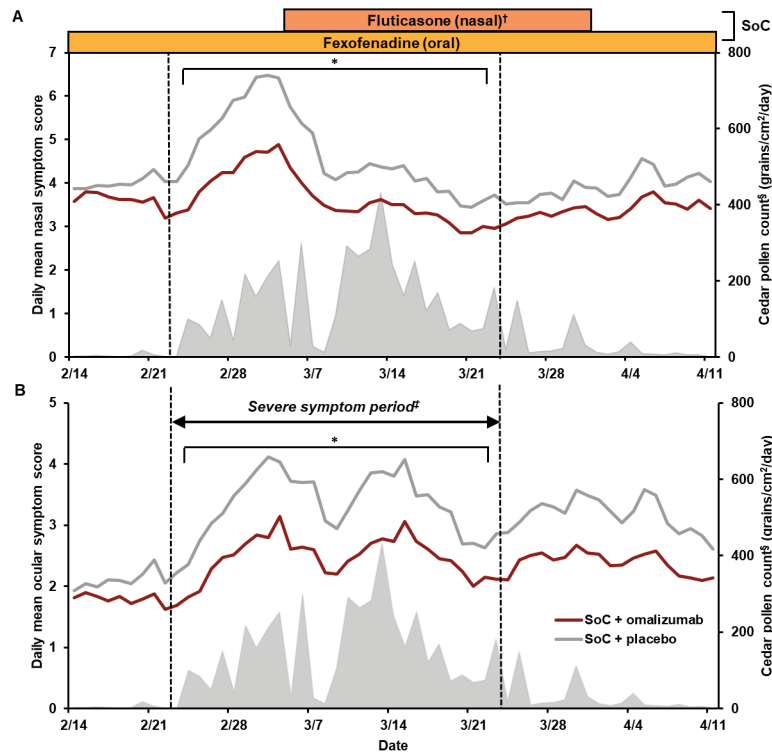


SoC, standard of care: Fexofenadine (oral) and fluticasone (nasal)

[†]Rescue medication: Fexofenadine (oral), tramazoline (nasal), and levocabastine (ocular)

[‡]Period with concomitant fluticasone (nasal): March 5 to April 1





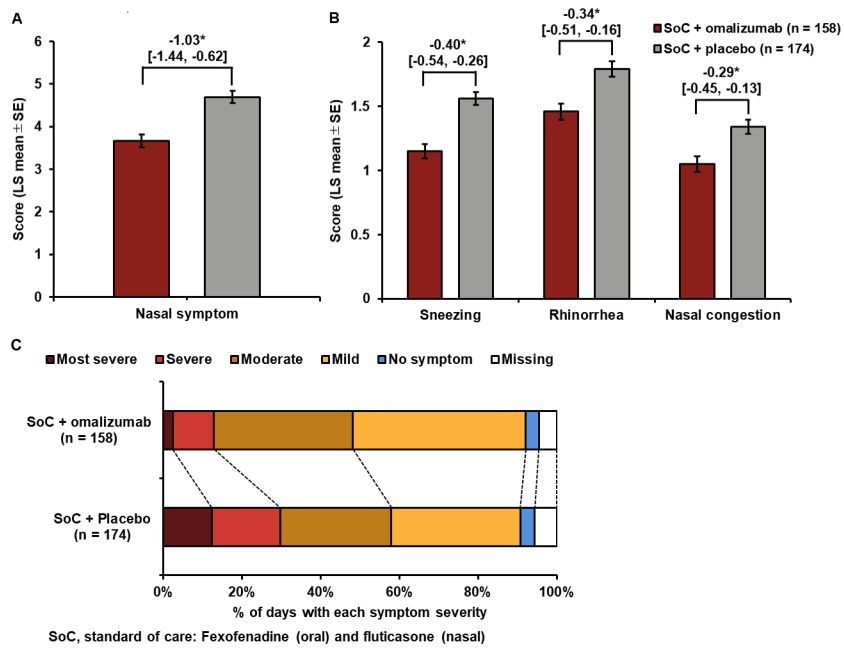
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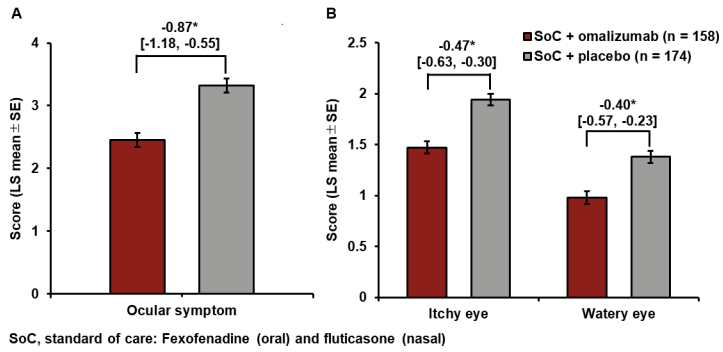
[†]Period with concomitant fluticasone (nasal): March 5 to April 1

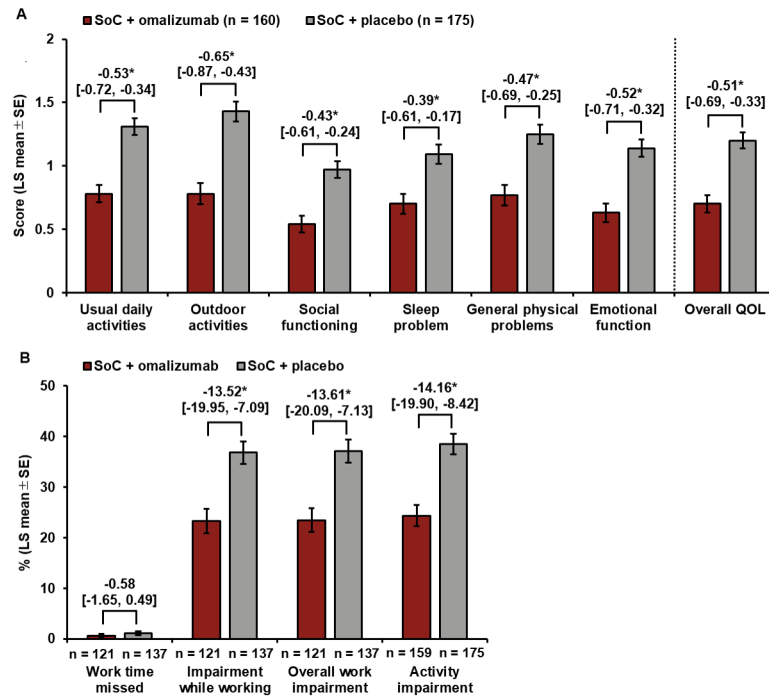
[‡]The severe symptom period (defined in the "Endpoint and assessments" section): February 23 to March 24.

^{*}Statistically significant differences ($p < 0.001$) between treatments were observed for both mean nasal symptom score and mean ocular symptom score during the severe symptom period (Detailed results are shown in Fig 4,A and Fig 5,A, respectively).

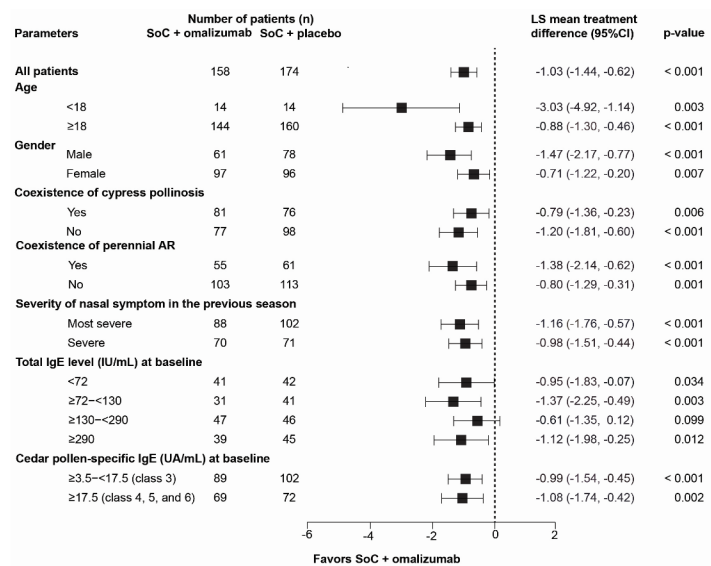
[§]Cedar pollen count measured with the Durham method in Tokyo (Chiyoda ward), which was provided as a public service from Tokyo Metropolis. A total of 5023 grains/cm² cedar pollen were scattered in Tokyo in 2018 season.







SoC, standard of care: Fexofenadine (oral) and fluticasone (nasal)



1 **Supplementary material**2 **TABLE E1 A.** Evaluation of nasal symptoms

Score	4	3	2	1	0
Paroxysmal sneezing (number of episodes of paroxysmal sneezing in a day)	≥ 21 times	20-11 times	10-6 times	5-1 times	0
Rhinorrhea (number of episodes of nose blowing a day)	≥ 21 times	20-11 times	10-6 times	5-1 times	0
Nasal congestion	Completely obstructed all day	Severe nasal congestion causing prolonged oral breathing in a day	Severe nasal congestion causing occasional oral breathing in a day	Nasal congestion without oral breathing	None

4 **TABLE E1B.** Classification of the severity of nasal symptom

Severity	Score	Paroxysmal sneezing or rhinorrhea (select more severe one)				
		4	3	2	1	0
Nasal congestion	4	Most severe	Most severe	Most severe	Most severe	Most severe
	3	Most severe	Severe	Severe	Severe	Severe
	2	Most severe	Severe	Moderate	Moderate	Moderate
	1	Most severe	Severe	Moderate	Mild	Mild
	0	Most severe	Severe	Moderate	Mild	No symptom

6 **TABLE E2.** Dosing table of omalizumab (or matching placebo)

Baseline IgE Concentration (IU/mL)	Body weight (Kg)									
	≥20~25	>25~30	>30~40	>40~50	>50~60	>60~70	>70~80	>80~90	>90~125	>125~150
≥30 ~ 100	75	75	75	150	150	150	150	150	300	300
>100 ~ 200	150	150	150	300	300	300	300	300	450	600
>200 ~ 300	150	150	225	300	300	450	450	450	600	375
>300 ~ 400	225	225	300	450	450	600	600	600	450	525
>400 ~ 500	225	300	450	450	600	600	375	375	525	600
>500 ~ 600	300	300	450	600	600	375	450	450	600	
>600 ~ 700	300	225	450	600	375	450	450	525		
>700 ~ 800	225	225	300	375	450	450	525	600		
>800 ~ 900	225	225	300	375	450	525	600			
>900 ~ 1000	225	300	375	450	525	600				
>1000 ~ 1100	225	300	375	450	600					
>1100 ~ 1200	300	300	450	525	600					
>1200 ~ 1300	300	375	450	525						
>1300 ~ 1500	300	375	525	600						

7 White cell: 4 weekly dosing, shaded cell: 2 weekly dosing

8 **TABLE E3.** Evaluation of ocular symptoms

Score	4	3	2	1	0
Itchy eye	More severe degree than score of 3	Frequently rubbing eye(s)	Occasionally rubbing eye(s)	Not to the extent of rubbing eye(s)	None
Watery eye	More severe degree than score of 3	Frequently wiping tears	Occasionally wiping tears	Not to the extent of wiping tears	None

9

1 **Supplemental figure Legends**

- 2 **FIG E1.** Mean nasal symptom scores during the severe symptom period by different subgroups
3 and treatment. The horizontal lines represent 95% CIs of the difference.