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# Omalizumab for the treatment of allergic rhinitis: a systematic review and meta-analysis*

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## Abstract

**Background**: Allergic rhinitis (AR), an IgE mediated inflammatory disease, significantly impacts quality of life of a considerable proportion of the general population. Omalizumab, a humanized monoclonal antibody against IgE, has been evaluated for both seasonal and perennial AR. We aimed to assess the efficacy and safety of omalizumab in randomized controlled trials (RCTs) in inadequately controlled AR.

**Methods**: We conducted a systematic literature search of RCTs evaluating the safety and efficacy of omalizumab in AR. We synthesized evidence for clinical improvement of AR symptoms, quality of life, reduction of the use of rescue medication, and adverse events.

**Results**: The systematic search returned 289 articles, of which 12 RCTs were eligible for data extraction and meta-analysis. Omalizumab reduced the Daily Nasal Symptom Severity Score (DNSSS) by a summary standardized mean difference of -0.41 points with large heterogeneity; omalizumab significantly reduced the DNSSS both in the 3 cedar pollen-induced AR trials by -0.97 points and to a lower extent in the remaining five non-cedar trials by -0.19 points. Omalizumab also improved the Daily Ocular Symptom Severity Score (DOSSS) by a summary standardized mean difference of -0.30 points with large heterogeneity; the Rhino-conjunctivitis Quality of Life Questionnaire by a summary standardized mean difference of -0.45 points with no heterogeneity and the mean daily consumption of rescue antihistamines by a summary standardized mean difference of -0.21 with large heterogeneity. No statistically significant difference in the occurrence of adverse events was observed between omalizumab and placebo.

**Conclusion**: Our findings further support the efficacy and safety of omalizumab in the management of patients with allergic rhinitis inadequately controlled with a conventional treatment.

**Key words**: Anti-IgE, daily nasal symptom severity score; daily ocular symptom severity score, rhino-conjunctivitis quality of life questionnaire

## Introduction

Allergic rhinitis (AR) is a symptomatic nasal disorder induced by inflammation in the nasal mucosa after allergen exposure. It´s a common medical condition presenting with high prevalence in the general global population with a substantial impact on the quality of life affecting almost all daily activities of patients [(1)]. Symptoms of AR include paroxysmal sneezing, watery rhinorrhea and nasal congestion and itching, frequently accompanied by ocular symptoms including itchy and watery eyes [(2)]. AR is a type I allergic disease mediated by allergen-specific IgE.

Apart from specific allergen immunotherapy, currently available therapeutic approaches, including mainly antihistamines and corticosteroids, focus on symptom relief and although they do not provide a permanent solution, they still remain first-line treatment [(3)]. The concept of targeting IgE through the use of anti-IgE antibodies for the management of allergic conditions has been the focus of intense research in the last decades. Although some additional anti-IgE treatments have been evaluated

in phase I and II trials in patients with AR, the development of such agents has largely been discontinued and, currently. the only anti-IgE biological treatment that is approved for the management of allergic conditions is omalizumab [4]. Omalizumab is a humanized monoclonal antibody against immunoglobulin E (IgE) which blocks the binding of IgE to high-affinity receptors (FceRI) on effector cells including mast cells and basophils [5] and has been used for the treatment of patients with allergic rhinitis and has been evaluated in several RCTs for allergic rhinitis [6]. However, the evidence that stems from the individual currently available randomized trials regarding the use of omalizumab in AR is not totally homogeneous.

In our previous work published in 2014, we found that the use of omalizumab was associated with symptom relief, decrease in rescue medication use, and improvement of quality of life in patients with inadequately controlled allergic rhinosinusitis [7]. Since then, additional RCTs have been published, providing new evidence available to update our previous findings. Thus, certain points have been raised that relate to the clinical aspects, the dosing schemes administered, and the clinical scores of the patients with inadequately controlled AR.

The aim of the present study was to update our previous work and evaluate the efficacy and safety of omalizumab in RCTs in inadequately controlled AR based on the currently available evidence evaluated through a systematic review and meta-analysis.

## Materials and methods

### Data sources and searches

We conducted a systematic literature search to identify RCTs which assessed the safety and efficacy of omalizumab in AR. Two reviewers independently searched MEDLINE (through PubMed) and the Cochrane Central Register of Controlled Trials (CENTRAL) from inception on September 30, 2020 and inconsistencies were resolved by a third reviewer. A search in PubMed was performed using the following algorithm "('omalizumab' OR 'anti-IgE' OR 'anti-immunoglobin E') AND ('rhinitis' OR 'allergic rhinitis') AND (random OR random* OR trial OR "randomised controlled trial" OR "randomized controlled trial" OR "clinical trial")" and in CENTRAL using the terms "('omalizumab' OR 'anti-IgE' OR 'anti-immunoglobin E') AND ('rhinitis' OR 'allergic rhinitis')".

All randomized trials that assessed subcutaneous omalizumab as treatment or pretreatment in patients with AR were considered eligible. All nonrandomized and quasi-randomized trials were excluded. We also excluded studies that assessed clinical outcomes unrelated to rhinitis, studies using an anti-IgE other than omalizumab, and studies which were not RCTs.

### Study outcomes

The assessed outcomes in this meta-analysis comprised clinical improvement of AR symptoms, use of rescue medication, rhinoconjunctivitis-related quality of life and the occurrence of adverse events. Studies, that assessed the safety and efficacy of omalizumab regarding the aforementioned outcomes, were included in the systematic review and meta-analysis regardless of the type and number of outcomes.

### Data extraction

From each eligible study, we recorded information about first author, publication year, journal, population characteristics, total and per-arm sample size, treatment indication, omalizumab and comparator dose, mode of administration and study duration. Moreover, we extracted information on rhinitis-related outcomes along with their effect estimates. Standardized mean differences (with the corresponding standard errors) were calculated for the continuous outcomes (Daily Symptom Severity Score, DSSS; Daily Nasal Symptom Severity Score, DNSSS; Daily Ocular Symptom Severity Score, DOSSS; Rescue Medication, RM; Rhino-conjunctivitis Quality of Life Questionnaire, RQoL) and Relative Risks (RRs) along with their Confidence Intervals (CIs) were calculated for Adverse Events (AE) that were assessed as binary outcomes. Concerning the methodological features of the included studies, we extracted information on randomization mode, allocation concealment and blinding.

### Risk of bias evaluation

The methodological quality and the risk of bias for the included studies were assessed using the Cochrane collaboration tool [8]. More specifically, we assessed the risk of bias for: selection (randomization and allocation concealment of the included trials), detection (blinding of outcome assessment), performance (blinding of study participants) and attrition (loss to follow-up).

### Data synthesis and analysis

We calculated the standardized summary mean differences and the relative risks (RR), along with the corresponding 95% CI, by pooling the study-specific estimates using fixed and random-effects models. The standardized mean difference indicated the mean change per SD allowing for the comparison of scores in different scales. The presence and the degree of heterogeneity were assessed with $I^2$ (ranging from 0% to 100%). When high heterogeneity was detected, it was further investigated through subgroup analysis. We further assessed possible small study effects (an indication of publication bias) by visual inspection of funnel plots and Egger test. All analyses were performed using Stata (version 14; StataCorp, College Station, TX, USA).

## Results

### Study selection and population characteristics

The systematic search returned 289 articles, 83 of which were selected for full text screening. Fourteen articles were considered eligible for data extraction and meta-analysis according to our criteria of eligibility; two articles [9, 10] were parts of another

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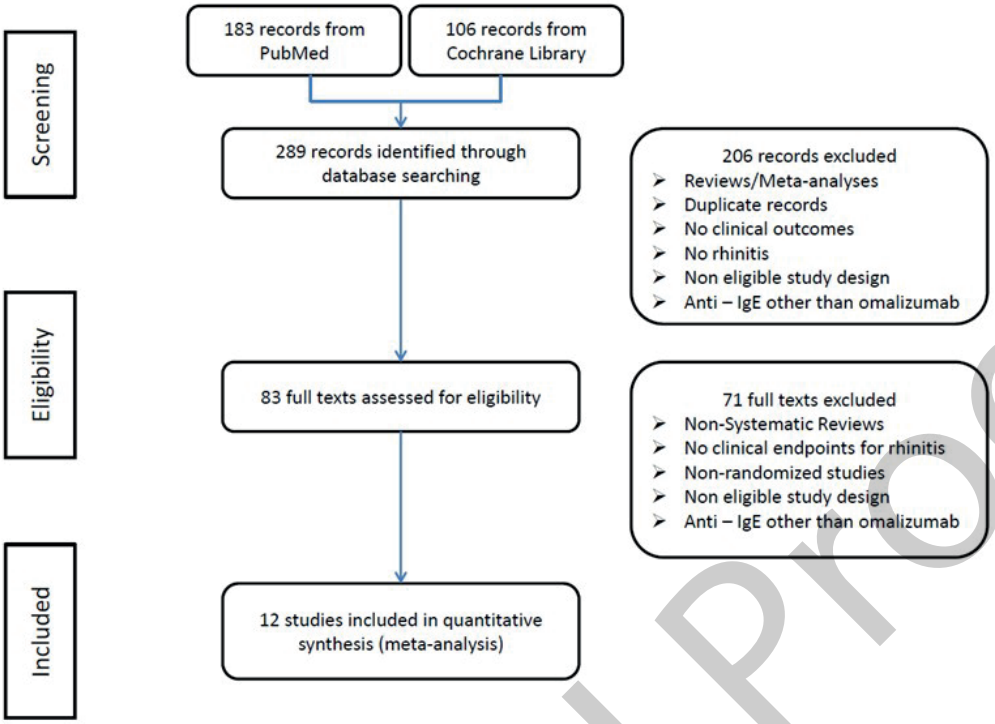


Figure 1. Flow chart of the study selection process.

of our included articles [11]. The publications of Bez et al., 2004 and Rolinck-Werninghaus et al., 2004 were found to be post hoc analyses of the study of Kuehr et al., 2002. The study of Bez et al., 2004 was excluded from further analyses as it did not contain any outcome of interest, while the study of Rolinck-Werninghaus et al., 2004 was used for the outcomes of interest which were not available in the study of Kuehr et al., 2002. Eventually, twelve studies were included in quantitative synthesis and meta-analysis. Figure 1 shows the flow chart of the study selection process. A summary of the characteristics of the included studies are presented in Table 1. Briefly, 4 trials were conducted in Europe, 4 in USA and 3 in Japan, assessing a total of 3,211 patients. Two trials included only pediatric patients, while 5 included only adult patients (>17 years of age). In 3 trials AR was indicated as birch/grass Seasonal Allergic Rhinitis (SAR) / Seasonal Allergic Rhino-Conjunctivitis (SARC) in 3 trials the AR indication was ragweed SAR and in 3 trials the AR indication was cedar SAR. In 5 trials the symptom severity range was from moderate to severe. Omalizumab was administered subcutaneously in all the trials every 2 or 4 weeks to provide either a fixed dose or a dose dependent on body weight and serum IgE levels (Table 1). The methodologic quality for the majority of studies found to be good (Supplementary Table 1). All studies were double blinded and almost all of them provided a sufficient description regarding the follow-up of the patients; 5 studies performed an intention-to-treat (ITT) analysis. Nevertheless, most of the studies did not report adequately any methodological measurements to ensure allocation concealment and blinding of outcome assessment.

### Outcomes of interest and evidence synthesis

All included studies provided information for a variation of outcomes. All in all, we were able to find enough data to proceed with a quantitative evidence synthesis for DNSSS, DOSSS, RM, RQoL and AE (Supplementary Table 1).

### Daily Nasal Symptom Severity Score (DNSSS)

DNSSS was calculated as the mean symptom score across all 4 nasal symptom severity components daily (sneezing, itchy, runny and stuffy nose), each scored by patients according to a 4-point scale (0, none; 1, mild; 2, moderate; 3, severe). Eight studies with a total of 2,136 randomized patients provided enough data to allow for a quantitative evidence synthesis based on the DNSSS. Overall, omalizumab statistically significantly reduced the DNSSS by a summary standardized mean difference of -0.41 points (95% CI, -0.61, -0.22; $p<0.001$; $I^2 = 93.2\%$) (Figure 2). A subgroup analysis by the specific AR indication showed that omalizumab in the 3 cedar pollen-induced AR trials statistically significantly reduced the DNSSS by a summary standardized mean difference of -0.97 points (95% CI, -1.43, -0.51; $p<0.001$; $I^2 = 80.3\%$), while in the remaining five non-cedar trials, DNSSS was also statistically significantly reduced, by a summary standardized mean difference of -0.19 points (95% CI, -0.25, -0.13; $p<0.001$; $I^2 = 1.6\%$) (Figure 2). No evidence of small study

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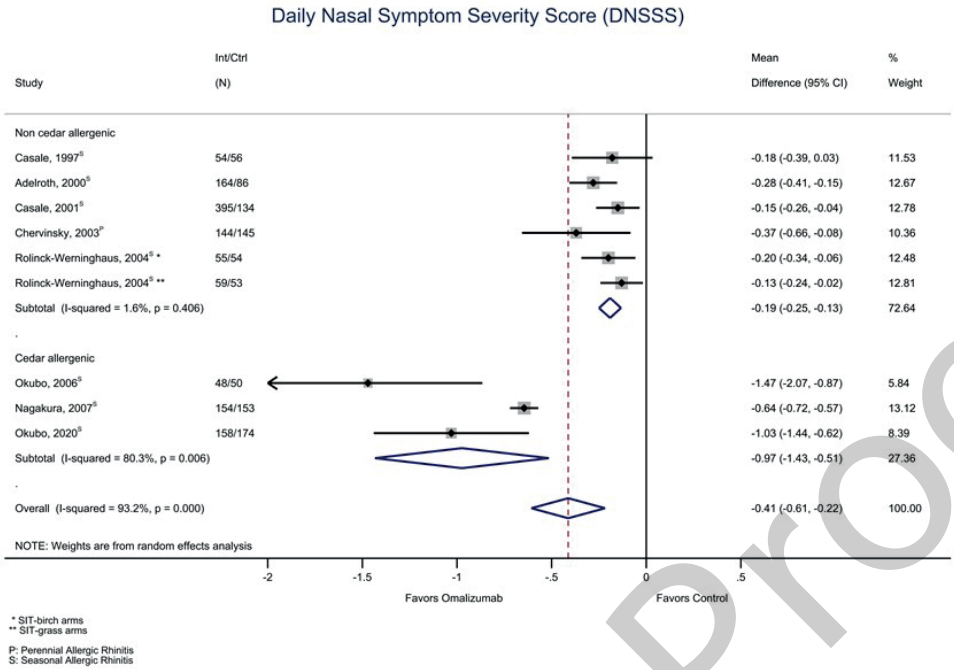


Figure 2. Forest plot of the meta-analysis of omalizumab for the DNSSS. The horizontal lines represent 95% CIs of the mean differences. Diamonds represent the meta-analysis summary effect estimate.

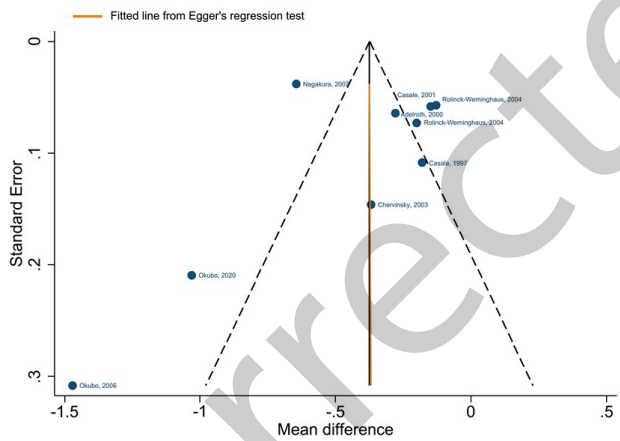


Figure 3. Funnel plot of the meta-analysis of omalizumab for the DNSSS. The Egger's test (p=0.994) indicates that there is no evidence of small study effect bias.

effects was observed, as Egger's test was not statistically significant (p=0.994) (Figure 3).

### Daily Ocular Symptom Severity Score (DOSSS)

DOSSS was calculated as the mean symptom score across all ocular symptom severity components daily (including itchy, watery, ore red eyes), each scored by patients according to a 4-point scale (0, none; 1, mild; 2, moderate; 3, severe). Four studies with 949 randomized patients provided enough data to allow for a quantitative evidence synthesis based on the DOSSS. Overall, omalizumab statistically significantly reduced the DOSSS score by a summary standardized mean difference of -0.30 points (95% CI, -0.50, -0.09; p=0.004; $I^2$ = 86.2%) (Figure 4).

### Use of rescue medication

The type of rescue medication (RM) varied across the eligible trials, including antihistamines, naphazoline nitrate, topical antihistamines, topical nasal corticosteroids, systemic corticosteroids, tramazoline hydrochloride and levocabastine hydrochloride. We assessed the use of RM in two different ways, depending on type of data that eligible studies provided. First, a daily mean score was calculated by adding the total number of different kinds of rescue medications used each day during the pollen season divided by the total number of days in the pollen season. Five studies with a total of 1,098 randomized patients provided enough data to allow for a quantitative evidence synthesis based on the RM as a daily mean score. In two studies [11, 12], rescue medication score was defined as daily usage on a 4-point scale (0= no rhinitis medication; 1= topical nasal, ocular, or lung treatment apart from corticosteroids; 2= systemic antihistamines; 3= systemic or topical corticosteroids for nose or lung). When more than one rescue medication was used on the same day, only the maximal score medication was recorded. In the other three studies [13-15], it was measured on a 4-point scale (0-3 points), but it was not described sufficiently how the score was generated. Overall, in the studies with appropriate data, omalizumab statistically significantly reduced the use of rescue

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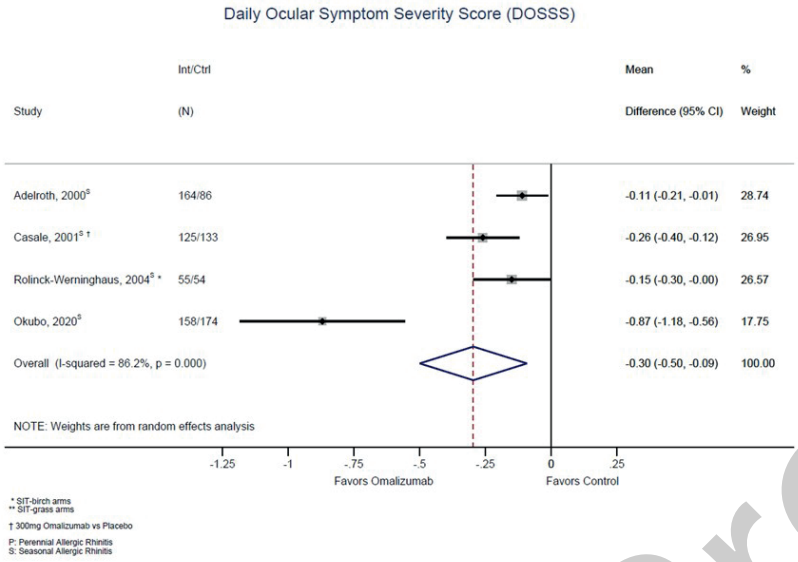


Figure 4. Forest plot of the meta-analysis of omalizumab for the DOSSS. The horizontal lines represent 95% CIs of the mean differences. Diamonds represent the meta-analysis summary effect estimate.

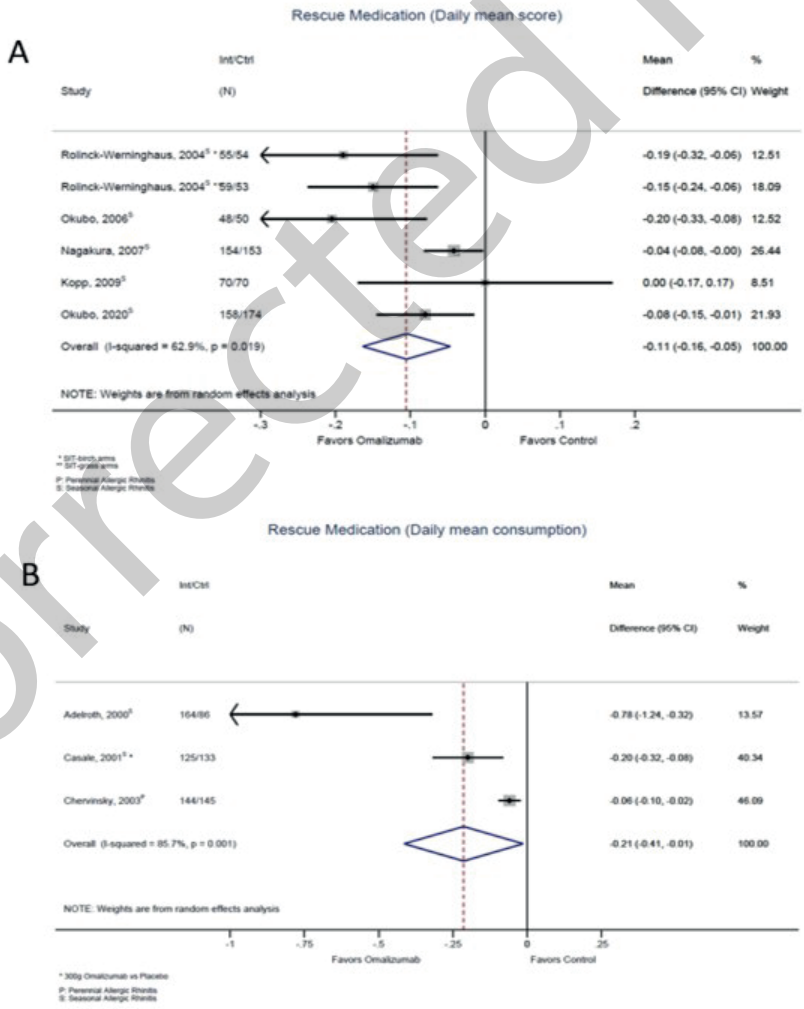


Figure 5. Forest plot of the meta-analysis of omalizumab for the RM (A) as daily mean score and (B) as daily mean consumption. The horizontal lines represent 95% CIs of the mean differences. Diamonds represent the meta-analysis summary effect estimate. In Kopp (2009) the patients received a specific allergen immunotherapy.

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Table 1. General Characteristics of included studies.

| Study | Location | Population age (year) | Indication | Symptom severity | N | N of arms | Omalizumab dose (SC) | Control | Intervention Duration |
|---|---|---|---|---|---|---|---|---|---|
| Casale, 1997[29] | USA | 18-66 | ragweed SAR | 1-2 | 240 | 4 | 0.15 mg/kg | Placebo | 12 weeks |
| Adelroth, 2000[16] | Scandinavia | 17-66 | birch SAR | NR | 251 | 2 | 300 mg | Placebo | 8 weeks |
| Casale, 2001[30] | USA | 12-75 | ragweed SAR | 2-3 | 536 | 4 | 50-300 mg | Placebo | 9 weeks |
| Kuehr, 2002[11] | Germany | 6-17 | birch, grass SAR | NR | 225 | 4 | 0.016 mg/kg/IgE | Placebo | 24 weeks |
| Chervinsky, 2003[17] | USA | 12-70 | mite, dog, cat PAR | 2-3 | 289 | 2 | 0.016 mg/kg/IgE | Placebo | 16 weeks |
| Vingola, 2004[31] | NR | 12-75 | PAA & PAR | 2-3 | 405 | 2 | 0.016 mg/kg/IgE | Placebo | 28 weeks |
| Casale, 2006[22] | USA | 18-50 | ragweed SAR | | 159 | 4 | 0.016 mg/kg/IgE | Placebo | 21 weeks |
| Okubo, 2006[14] | Japan | 20-64 | cedar SAR | 2-3 | 100 | 2 | 150-375 mg | Placebo | 12 weeks |
| Nagakura, 2007[13] | Japan | 20-64 | cedar SAR | 2-3 | 308 | 2 | 0.016 mg/kg/IgE | suplatast tosilate | 12 weeks |
| Kopp, 2009[12] | Germany | 11-46 | SAA & SAR | NR | 140 | 2 | 0.016 mg/kg/IgE | placebo | 18 weeks |
| Kamin, 2010[23] | Germany | children | birch, grass SARC | NR | 221 | 4 | 0.016 mg/kg/IgE | placebo | 24 weeks |
| Okubo, 2020[¥15] | Japan | 12-75 | cedar SAR | 3 | 337 | 2 | 75-600 mg | placebo* | 12 weeks |

SAA: Severe Allergic Asthma; SAR: Seasonal Allergic Rhinitis; PAA: Perennial Allergic Asthma; PAR: Perennial Allergic Rhinitis; ARC: Allergic Rhino-Conjunctivitis. NR: No Reference; SC: Subcutaneous; Symptom Severity: 1=mild, 2=moderate, 3=severe. [¥] In the Okubo 2020 trial all patients received concomitant antihistamines and nasal corticosteroids as standard of care treatment. *Standard of care treatment + placebo.

| Study | No of Serious Adverse Events | Serious Adverse Events Details | Comments |
|---|---|---|---|
| Casale, 1997[29] | 1 | Colitis | Unrelated to the study drug according to authors |
| Adelroth, 2000[16] | 0 | | |
| Casale, 2001[30] | 0 | | |
| Kuehr, 2002[11] | 0 | | |
| Chervinsky, 2003[17] | NR | | |
| Vingola, 2004[31] | 3 | Acute appendicitis, mild chest pain, mild depression | |
| Casale, 2006[22] | 1 | NR | |
| Okubo, 2006[14] | 1 | Colitis ulcerative | Unrelated to the study drug according to authors |
| Nagakura, 2007[13] | 1 | Ureteric calculus | Unrelated to the study drug according to authors |
| Kopp, 2009[12] | NR | | |
| Kamin, 2010[23] | 0 | | |
| Okubo, 2020[¥15] | 1 | Testicular neoplasm | Unrelated to the study drug according to authors |

NR: Not Reported. [¥] In the Okubo (2020) trial all patients received concomitant antihistamines and nasal corticosteroids as standard of care treatment.

medication mean score by a summary standardized mean difference of -0.11 points (95% CI: -0.16, -0.05; p<0.001; $I^2$ = 62.9%) (Figure 5a).

Moreover, we assessed the use of rescue medication as daily mean consumption, i.e. the average daily rescue antihistamine tablets consumed by patients. Three studies with 797 randomized patients provided enough data to allow for a quantitative evidence synthesis based on the use of rescue medication assessed as mean daily consumption. Overall, omalizumab statistically significantly reduced the mean daily consumption of rescue medication with antihistamines by a summary standardized mean difference of -0.21 (95% CI, -0.41, -0.01; p=0.036; $I^2$ = 85.7%) (Figure 5b).

**Rhino-conjunctivitis Quality of Life questionnaire (RQoL)**

In most studies, the study participants were asked to fill a questionnaire before and after the intervention to evaluate the efficacy of treatment. The questions pertained a variation of out-

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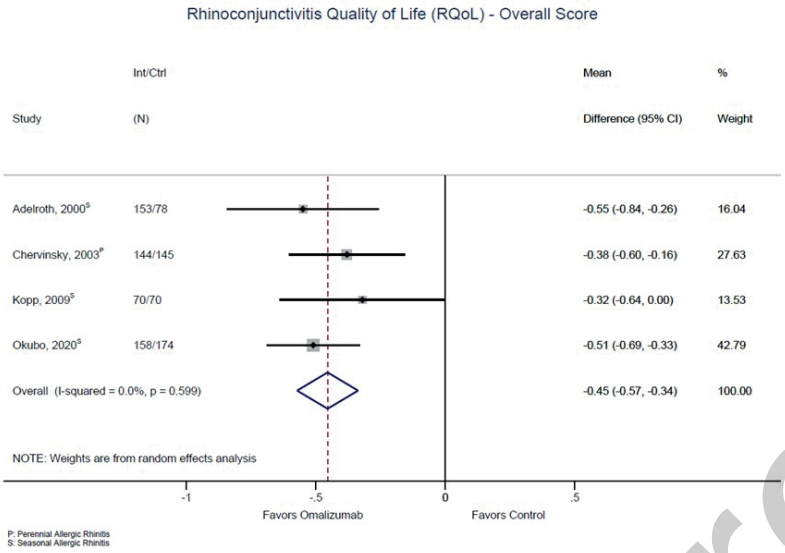


Figure 6. Forest plot of the meta-analysis of omalizumab for the RQoL. The horizontal lines represent 95% CIs of the mean differences. Diamonds represent the meta-analysis summary effect estimate. In Kopp (2009), patients received a specific allergen immunotherapy.

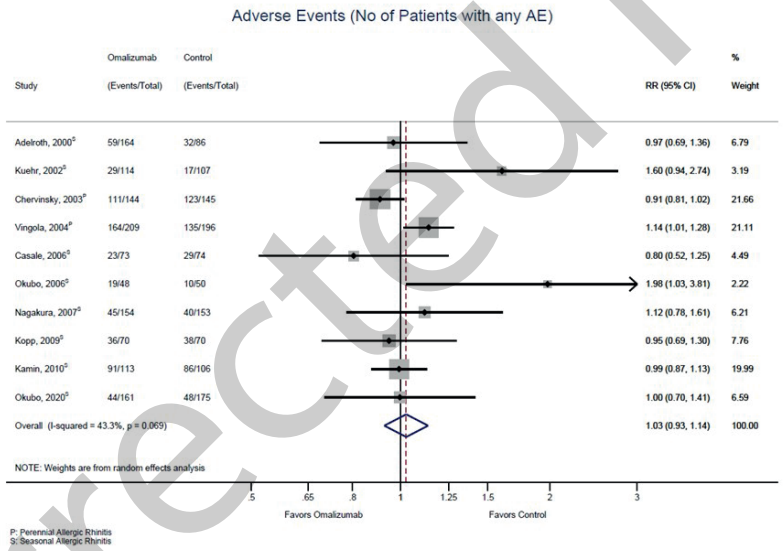


Figure 7. Forest plot of the meta-analysis of omalizumab for the AEs. The horizontal lines represent 95% CIs of the RRs. Diamonds represent the meta-analysis summary effect estimate. In Kuehr (2002), Casale (2006), Kopp (2009) and Kamin (2010), the patients received a specific allergen immunotherapy.

comes including sleep impairment, usual daily activity limitations, emotional functions, symptoms meaningful change and an overall score, which reflected the evaluation of the overall efficacy of the treatment. Four studies with 992 randomized patients provided enough data on an overall score of RQoL that allowed for a quantitative synthesis. The overall score was measured in a 5-point scale in 3 studies [12, 15, 16] and in a 7-point scale in 1 study [17]. In all 4 studies, the respective score ranged from low to high score values indicating excellent to poor effectiveness of treatment respectively. Omalizumab statistically significantly reduced the RQoL by a summary standardized mean difference of -0.45 (95% CI, -0.57, -0.34; $p<0.001$; $I^2 = 0\%$) (Figure 6).

### Adverse events (AE)

Ten studies provided enough information on the occurrence of AEs. No statistically significant difference on the occurrence of AE was observed between the use of omalizumab vs. placebo (RR=1.03; 95% CI, 0.93, 1.14; $p=0.618$; $I^2 = 43.3\%$) (Figure 7). Supplementary Table III presents the AEs of the included trials classified in system organ classes based on Medical Dictionary for Regulatory Activities version 23 (MedDRA v.23). Serious AEs of the included trials are presented in Table 2.

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## Discussion

In this systematic review and meta-analysis, we evaluated the efficacy and safety of omalizumab in the treatment of AR. Our systematic review retrieved 12 RCTs, with a total of 3,211 patients. The meta-analysis showed that, treatment with omalizumab significantly improved the nasal and ocular symptom scores, as well as the disease-specific quality of life and reduced the need of rescue medication in patients with AR, without any signal for increased adverse events compared to placebo.

We observed that the improvement in nasal symptom score was higher in the three cedar pollen-induced allergic rhinitis trials, which were conducted in Japan, and particularly in two of them [14, 15] this improvement between treatment groups exceeded the previously reported minimal clinically relevant difference (MCID) of 0.87 points [18], as was the overall mean subtotal difference of these studies reaching -0.97 points, in contrast to the -0.19 points in the rest of the studies. Cedar pollinosis constitutes an important medical problem in Japan. Its prevalence was increased by almost 10% from 1998 (19.6%) to 2008 (29.8%) [19]. Furthermore, a more recent study indicated that the prevalence of cedar pollinosis in Japan had been estimated to be over 40% [20]. Importantly, approximately 50% of patients with diagnosed cedar pollinosis develop severe seasonal symptoms, with a significant impact on their daily lives and the need for additional treatments [21]. The greater efficacy of anti-IgE treatment in patients with cedar pollinosis may reflect the significant burden of disease and the central role of IgE in this form of allergic rhinitis. However, based on the available data in this meta-analysis, we cannot exclude potential differences in the clinical management of allergic rhinitis in Japanese patients, including the use of intranasal corticosteroids. The clinical heterogeneity between studies with cedar allergen and studies with other allergens may also drive the visual asymmetry observed in the funnel plot of our analysis (Figure 3). The 3 Japanese studies (with cedar allergen) present a smaller mean difference and thus these studies are on the left side of the plot while the rest of the studies form a cluster on the right side of the plot.

Omalizumab treatment reduced significantly the daily use of rescue medication and improved quality of life compared to placebo. The overall mean improvement in RQoL of 0.45 points was close to the minimal clinically important difference that has been previously reported as being 0.5 points [18]. Interestingly, the mean treatment effect of omalizumab on RQoL in two of the trials that assessed this outcome [15,16] exceeded the minimal clinically important difference (reaching -0.55 and -0.51 points, respectively).

The comparator of omalizumab was placebo in all but one of the earlier trials [13] in which suplatast tosilate was given to the patients randomized in the control arm, while in 4 other trials [11, 12, 22, 23], the patients received a specific allergen immunotherapy. More importantly, in the trial by Okubo and co-authors 2020 [15], the latest of the omalizumab trials in patients with cedar pollinosis, patients received concomitant standard-of-care medications (antihistamines and nasal corticosteroids) in both treatment arms (omalizumab and placebo). As previously mentioned, in this trial, the mean effect of omalizumab exceeded the MCID for daily nasal symptoms score and for rhinitis-related quality of life, suggesting clinically relevant efficacy of omalizumab on top of standard-of-care medication in a severe form of the disease that significantly impacts the daily life of patients. A potential reason for the pronounced efficacy of omalizumab in patients with cedar pollinosis may have been the severity of AR and the causative allergens. In the study by Okubo and colleagues, approximately 60% had most severe and 40% had severe nasal symptoms, while approximately 48% had seasonal cedar pollinosis and 35% had perennial AR [15] and in all 3 studies the patients had a long-standing history of AR with a mean duration over 10 years [13-15], that exceeded 15 years in the latest trial [15]. Based on the results of the study by Okubo and colleagues [14], omalizumab was approved [24] for severe seasonal AR that is inadequately controlled by standard-of-care medication in Japan. In the same line, a recent meta-analysis included 16 RCTs of patients with poorly controlled seasonal and perennial AR and showed that the omalizumab had a statistically significant difference in reduced use of rescue drugs, improved symptoms, and improved quality of life [25]. However, this meta-analysis does not include the recent study from Okubo and colleagues [15] that was a large trial with standard of care treatment in the control arm.

Apart from specific allergen immunotherapy that remains the only disease modifying treatment, currently available therapeutic approaches, including mainly oral or intranasal antihistamines and intranasal corticosteroids, focus on symptom relief; however, adherence represents a major disadvantage for topical therapies [3]. In a recent meta-analysis, the addition of oral antihistamines to intranasal corticosteroids did not lead to a change in total nasal symptom score (mean difference -0.10, 95%CI -0.27 to 0.08), while the combination of a nasal antihistamine with nasal corticosteroid was superior to nasal corticosteroids alone (mean difference -0.66, 95%CI -0.93 to -0.40) [26], potentially suggesting that intranasal therapy is more effective than oral treatment for nasal disease. Importantly, 50% of patients with diagnosed cedar pollinosis develop severe seasonal symptoms, with a significant impact on their daily lives and the need for additional treatments, as omalizumab, since standard of care treatment (including antihistamines and intranasal corticosteroids) is not effective. Additionally, the recommended treatment strategy for AR from the ARIA guideline [27] 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 provide additional benefit. Omalizumab treatment provided a clinically meaningful efficacy, exceeding the MCID for the nasal symptom score in two

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of the cedar pollen-induced allergic rhinitis trials in Japan [14, 15], with the latest showing this benefit on top of appropriate SoC treatment [15]. In the absence of head-to head studies, we need to acknowledge that other available treatments, including intranasal corticosteroids and fixed dose combinations of intranasal corticosteroids and antihistamines, have reached similar and sometimes greater improvement in clinically relevant parameters vs placebo - indirectly compared to some omalizumab clinical studies [32]. DNSSS reduction did not reach the MCID of 0.87 and the improvement of RQLQ did not reach statistical significance in this analysis, however we need to remember that in one clinical trial all patients received concomitant antihistamines and nasal corticosteroids as standard of care treatment and in four trials patients received concomitant allergen immunotherapy. Given the higher cost of omalizumab treatment, the cost-effectiveness of this intervention needs to be evaluated in appropriately designed health economics analyses.

Overall, the results of the present meta-analysis further support the conclusions of our previous work [7], reinforcing them by the inclusion of an important number of more recent studies involving a significantly larger number of participants. The fact that omalizumab continues to present a comparable adverse effects profile to placebo, combined with superior efficacy, further supports a favorable benefit-risk profile for this medication in patients with severe AR inadequately controlled with conventional treatments.

Our study has certain limitations. Firstly, considerable between-study heterogeneity was observed. This was expected due to the different populations of which, our included trials were consisted of. As mentioned before, the improvement of nasal symptom score was higher in the 3 trials that held in Japan, where the AR prevalence and severity, especially in the form of cedar pollinosis, is higher. Additionally, differences in the baseline severity of the disease; different prevalence of patients with other comorbidities, such as asthma, conjunctivitis, and atopic dermatitis; difficulties in the comparability of different scores used; differences in omalizumab dose and dosing may have limited the accuracy of this meta-analysis Finally, our findings come from published RCTs, thereby excluding real world evidence, like the recently published paper by Cavaliere and co-workers on long term efficacy of omalizumab in AR28. Furthermore, publication and language bias are a major concern when dealing with efficacy trials.

## Conclusion

In this meta-analysis, we have demonstrated that treatment with omalizumab in patients with allergic rhinitis significantly improved the nasal and ocular symptom scores and QoL, reduced the use of rescue medication, with a safety profile comparable to placebo. Our findings further support the efficacy and safety of omalizumab in the management of patients with allergic rhinitis inadequately controlled with conventional treatment. The potential benefits of omalizumab need to be considered in the context of access of therapy and cost effectiveness.

## List of abbreviations

AE- Adverse event; AR- Allergic rhinitis; CI- Confidence interval; DOSSS - Daily Ocular Symptom Severity Score; DNSSS - Daily Nasal Symptom Severity Score; DSSS - Daily Symptom Severity Score; RM - Rescue Medication; RQLQ- Rhino-conjunctivitis Quality of Life Questionnaire; RR – Relative Risk; QoL- Quality of life; SoC- Standard-of-care

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## Authorship contribution

ST, GD, FK, EE, PO and KK contributed to the design and implementation of the research, to the analysis of the results and to the writing of the manuscript. GD and FK contributed to the analysis of the results. ST, GD, PO and KK contributed amendments to the manuscript and revised it critically. All authors approved the final version of the manuscript to be published.

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## Conflict of interest

ST, GN, FK and EE do not disclose any potential sources of conflict of interest. PO is a shareholder and owns stock options in Novartis AG and is employed by Novartis AB. KK was an employee and shareholder of Novartis Pharma AG until 31.10.2018. He has received honoraria for presentations and consultancy fees from AstraZeneca, Boehringer Ingelheim, Chiesi, CSL Behring, ELPEN, GSK, Menarini, Novartis, Sanofi Genzyme and WebMD. His department has received funding and grants from AstraZeneca, Boehringer Ingelheim, Chiesi, Innovis, ELPEN, GSK, Menarini, Novartis and NuvoAir.interest.

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**This manuscript contains online supplementary material**

## SUPPLEMENTARY MATERIAL

Supplementary Table 1. Assessment of methodological quality.

| Study | Randomization, done/described | Allocation concealment, done/described | Blinding, done/described | Outcome assessment blinding, done/described | Loss to follow-up, described/ITT analysis |
|---|---|---|---|---|---|
| Casale, 1997 | Yes/clear | No/clear | Yes/clear | Yes/unclear | Yes/no |
| Adelroth, 2000 | Yes/unclear | No/clear | Yes/unclear | No/unclear | Yes/yes |
| Casale, 2001 | Yes/clear | No/clear | Yes/clear | Yes/clear | Yes/no |
| Kuehr, 2002 | Yes/unclear | No/clear | Yes/unclear | No/unclear | Yes/yes |
| Chervinsky, 2003 | Yes/clear | Yes/clear | Yes/clear | Yes/unclear | Yes/yes |
| Vingola, 2004 | Yes/clear | No/clear | Yes/unclear | No/unclear | Yes/yes |
| Casale, 2006 | Yes/unclear | No/unclear | Yes/unclear | Yes/unclear | Yes/no |
| Okubo, 2006 | Yes/unclear | No/clear | Yes/unclear | No/clear | Yes/no |
| Nagakura, 2007 | Yes/unclear | No/clear | Yes/unclear | No/clear | Yes/no |
| Kopp, 2009 | Yes/clear | No/unclear | Yes/unclear | No/unclear | Yes/no |
| Kamin, 2010 | Yes/unclear | No/unclear | Yes/unclear | No/unclear | No/no[†] |
| Okubo, 2020 | Yes/yes | No/unclear | Yes/unclear | No/clear | Yes/yes |

ITT: Intention to treat; [†]Safety assessment only

Supplementary Table 2. Outcomes per study.

| Study | DNSSS | DOSSS | DSSS | DNSMS | DOSMS | SL | RM | RQLQ | AE |
|---|---|---|---|---|---|---|---|---|---|
| Casale, 1997 | * | | | | | | + | + | + |
| Adelroth, 2000 | * | + | | | | | + | + | + |
| Casale, 2001 | * | + | + | | | | + | + | + |
| Kuehr, 2002 | | | + | | | * | + | | + |
| Chervinsky, 2003 | * | | | | | | + | + | + |
| Rolinck-Werninghaus, 2004 [¥] | * | + | | | | | + | | |
| Vingola, 2004 | | | | | | | + | * | + |
| Casale, 2006 | | | * | | | | | | + |
| Okubo, 2006 | + | + | | * | + | | + | | + |
| Nagakura, 2007 | + | + | | * | + | | + | | + |
| Kopp, 2009 | | | | | | * | + | + | + |
| Kamin, 2010 | | | | | | | | | * |
| Okubo, 2020 [1] | * | + | | | | | + | + | + |

[¥] Sub-analysis of Kuehr study; * Primary Outcome; + Secondary Outcome; [1] In the Okubo 2020 trial all patients received concomitant antihistamines and nasal corticosteroids as standard of care treatment.

DSSS: Daily Symptom Severity Score; DNSSS: Daily Nasal Symptom Severity Score; DOSSS: Daily Ocular Symptom Severity Score; DNSMS: Daily Nasal Symptom Medication Score; RM: Rescue Medication; RQLQ: Rhino-conjunctivitis Quality of Life Questionnaire; SL: Symptom Load; AE: Adverse Events.

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Supplementary Table 3. Reported Adverse Events of included classified in system organ classes based on Medical Dictionary for Regulatory Activities version 23 (MedDRA v.23).

| Row Labels | Any Adverse Event | Cardiac Disorders | Ear and Labyrinth Disorders | Gastrointestinal disorder | General disorders and administration site condition | Immune System Disorders | Infections and infestations | Investigations | Musculoskeletal and Connective Tissue Disorders | Nervous system disorders | Respiratory, thoracic and mediastinal disorders | Skin and subcutaneous tissue disorder |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| Adelroth, 2000 | 1 | | | | 3 | | | | | | | 9 |
| Casale, 1997 | | | | | 6 | | 1b,2 | | | 1 | | |
| Casale, 2001 | | | | | 5,6 | | 1a,1c,2 | 1,2 | 1,2 | 1 | 3,6 | |
| Casale, 2006 | 1 | 1,2 | | | 5,6 | | | | | 1 | 8 | 1,6,7,9 |
| Chervinsky, 2003 | 1 | | | | 6 | | 1a,1c,2 | | | 1 | 6,7 | |
| Kamin, 2010 | 1 | | 1 | 1 | 3 | | 1b | | | 1 | 1 | 2 |
| Kopp, 2009 | 1 | | | | 3 | | 2 | | | 1 | 3,6 | |
| Kuehr, 2002 | 1 | | 2 | 3 | 2,3,5 | 1 | 1a,1c,2 | | | 1 | 2-5,7 | 4,7 |
| Nagakura, 2007 | 1 | | | 1 | 3,4 | | | | | 1,2 | | 2 |
| Okubo, 2006 | 1 | | | 2,3 | 1,2,3,6 | | | | | 1 | | 3,5,8 |
| Okubo, 2020[¥] | 1 | | | | | | 1c,2 | | | | | |
| Vingola, 2004 | 1 | | | | | | 1a,1c,2 | | | 1 | 6 | |
| Okubo, 20201 | * | + | | | | | + | + | + | | | |
| Number of studies | 10 | 1 | 2 | 4 | 10 | 1 | 8 | 1 | 1 | 10 | 7 | 6 |

| | |
|---|---|
| Any Adverse Event: | 1=Overall |
| Cardiac Disorders: | 1=Angioedema, 2=Mean drop of BP>=15mm |
| Ear and Labyrinth Disorders: | 1=Earache, 2=Ears/vascular |
| Gastrointestinal disorder: | 1=Any, 2=Colitis ulcerative, 3=Diarrhea |
| General disorders and administration site condition: | 1=Fatigue, 2=Fever, 3=Injection Site Reaction, 4=Malaise, 5=Nausea, 6=Pain |
| Immune System Disorders: | 1=Peripheral Swelling |
| Infections and infestations: | 1=Infection (1a=Respiratory, 1b=Undescribed, 1c=Viral), 2=Pharyngitis/ Nasopharyngitis |
| Investigations: | 1=Special Senses, 2=Weight Increase |
| Musculoskeletal and Connective Tissue Disorders: | 1=Arthralgia, 2=Sprains and Strains |
| Nervous system disorders: | 1=Headache, 2=Somnolence |
| Respiratory, throracic and mediastinal disorders: | 1=Any, 2=Asthma, 3=Cough, 4=Dyspnea, 5=Rhinitis, 6=Sinusitis, 7=Sore Throat, 8=Wheezing |
| Skin and subcutaneous tissue disorder: | 1=Anaphylaxis, 2=Any, 3=Dry skin, 4=Eczema, 5=Edema, 6=Flushing, 7=Pruritus, 8=Rash, 9=Urticaria |

[¥] In the Okubo 2020 trial all patients received concomitant antihistamines and nasal corticosteroids as standard of care treatment.

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