

Influence of prolonged treatment with omalizumab on the development of solid epithelial cancer in patients with atopic asthma and chronic idiopathic urticaria: A systematic review and meta-analysis

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Abstract

Objective: We investigated whether prolonged treatment with omalizumab influences development or progression of solid epithelial cancer in patients with atopic asthma or chronic idiopathic urticaria.

Design: Systematic review and meta-analysis of intervention and observational studies. Randomized controlled trials were assessed for risk of bias using the Cochrane Risk of Bias tool, comparative observational studies were assessed using the Newcastle-Ottawa Scale, and non-comparative observational studies were assessed using the Joanna Briggs Institute Checklist for Prevalence Studies.

Data sources: We searched MEDLINE, EMBASE, Cochrane Library and grey literature for eligible studies to November 2017. All searches were updated in January 2019.

Eligibility criteria for included studies: Randomized, quasi-randomized, controlled clinical trials and observational studies were included if they involved patients ≥ 12 years with moderate-to-severe persistent asthma or chronic idiopathic urticaria treated with omalizumab for ≥ 40 weeks. Eligible comparators included standard of care, placebo, cromoglycate or no treatment.

Results: One hundred and sixty seven unique studies were eligible for inclusion; however, only twelve (7.2%, $n = 11\,758$) reported any outcome of interest, none of which involved patients with urticaria. 195 cancer events were reported. We found no statistically significant increase in the odds of study-emergent solid epithelial cancer in patients randomized to long-term treatment with omalizumab compared to standard of care (Peto OR: 0.65, 95% CI: 0.11, 3.74, $I^2 = 41\%$). Less than one per cent of participants of non-comparative observational studies ($n = 2350$) were diagnosed with a solid epithelial tumour (meta-proportion: 0.86% [95% CI: 0.24, 1.86%, $I^2 = 56\%$]). In the only comparative observational study reporting on cancer, the proportion of study-emergent solid epithelial tumour events was nearly identical in both study groups (omalizumab: 2.3%, standard of care: 2.2%).

Conclusions: There is insufficient evidence to determine whether long-term treatment with omalizumab influences development or progression of solid epithelial cancer in these patient populations.

PROSPERO registration # CRD 42018082211.

KEYWORDS

anti-IgE, asthma, atopy, cancer, systematic review, urticaria

1 | INTRODUCTION

Immunoglobulin E (IgE) is known to play a key role in mediating atopic Th2-associated conditions, including atopic asthma and chronic idiopathic urticaria (CIU).¹ IgE-bearing cells are found in the nasal or bronchial mucosa during the sensitization phase to aeroallergens and this sets the stage for their activation during subsequent allergen exposure.²⁻⁴ When an antigen binds to the IgE variable regions of two adjacent IgE antibodies on a mast cell, their receptors become physically cross-linked. The subsequent uptake of calcium ions leads to degranulation and release of pro-inflammatory mediators such as histamine, tryptase, leukotrienes and prostaglandins.^{4,5} These mediators are responsible for the symptoms of an immediate allergic reaction and can also contribute to late reactions that occur 4 to 8 hours after an immediate response.^{3,4,6}

Omalizumab is a recombinant humanized monoclonal antibody that binds circulating IgE.^{7,8} Studies in patients with atopic asthma have demonstrated that omalizumab decreases serum IgE levels in a dose-dependent manner and prevents allergen-induced bronchoconstriction during both the early- and late-phase responses to inhaled allergen.⁹⁻¹² Serum-free IgE is rapidly reduced after omalizumab administration, and the expression of high-affinity receptors is significantly reduced after 3 months of treatment.¹³

Omalizumab is indicated for patients with allergic asthma whose symptoms remain uncontrolled despite conventional treatment with inhaled corticosteroids, long-acting beta-agonists and leukotriene receptor antagonists.¹⁴⁻¹⁷ In 2003 and 2005, respectively, the United States Food and Drug Administration (US FDA) and Health Canada approved the use of omalizumab, a recombinant humanized monoclonal antibody, for the treatment of moderate-to-severe persistent asthma in individuals aged 12 years or older who develop a positive skin test, or have *in vitro* reactivity, to a perennial aeroallergen and are inadequately controlled with inhaled corticosteroids.⁸ In 2005, The European Medicines Agency approved omalizumab for use in patients with severe persistent allergic asthma aged 6 years and older.¹⁸ More recently (2014), the US FDA and Health Canada approved its use in individuals aged 12 years or older with CIU who remain symptomatic despite treatment with an H1 antihistamine.¹⁹

There is evidence to support the existence of an innate anti-tumour immune surveillance mechanism involving cytotoxic IgE antibodies and mast cells.^{20,21} Given that omalizumab selectively binds to free circulating IgE, it is conceivable that long-term treatment with omalizumab may impair these protective immunologically mediated

anti-tumour mechanisms in atopic patients and may theoretically increase predisposition to development of malignancy.

At least one study²² found that long-term treatment with omalizumab was not associated with an increased risk of cancer (after a five-year median follow-up period); however, Li et al²³ concluded the study's findings were unable to rule out cancer risk due to several study limitations. In the light of this, we completed a systematic review of published and unpublished evidence to investigate whether prolonged treatment with omalizumab influences the development or progression of solid epithelial cancer in patients (≥ 12 years of age) with atopic asthma or CIU. We focused on this type of malignancy because tissue-resident mast cells are enriched in boundary tissues, such as skin and mucosal membranes (eg respiratory and gastrointestinal tracts),²⁴ and are found in abundance at the margin of many solid tumours.²¹

2 | METHODS

The study protocol was registered with PROSPERO (CRD 42018082211) prior to the start of review, and this manuscript was prepared in accordance with the PRISMA checklist for systematic reviews and meta-analysis (Appendix S1).

2.1 | Search strategy

An experienced medical information specialist developed and tested the strategy, which was peer-reviewed using the PRESS Checklist.²⁵ MEDLINE (OVID) and EMBASE (OVID), including Epub Ahead of Print and In-Process & Other Non-Indexed Citations and the Cochrane Library (Wiley), were searched on 23 November 2017 (Appendix S2). A literature search update was completed in January 2019 (Appendix S3). Search strategies used a combination of controlled vocabulary (eg 'omalizumab', 'randomized controlled trial', 'cohort studies') and keywords (eg 'Xolair', 'RCT', 'observational study'). Vocabulary and syntax were adjusted across databases. When possible, animal-only, opinion-pieces and conference abstracts were removed. Focused grey literature searches were conducted on ClinicalTrials.gov and the International Clinical Trials Registry Platform (ICTRP) search portal for ongoing and completed clinical trials. The US FDA web site was searched for clinical reviews and regulatory reports, and we obtained redacted Medical Reviews conducted by Health Canada.

2.2 | Eligibility criteria

Specific details regarding the populations, intervention, comparators, outcomes, study design and timeframe of interest to this review are provided in Appendix S4. We included both published and unpublished interventional (eg randomized controlled trials (RCTs)) and observational (eg cohort and case control) studies of adults and adolescents (≥ 12 years) with chronic idiopathic/spontaneous urticaria (CIU/CSU) or moderate-to-severe persistent allergic asthma who were treated with long-term (continuous) omalizumab. Interventional studies were eligible if the final dose of omalizumab was administered at 48 weeks or longer and observational studies were eligible if participants were treated with omalizumab for a minimum of 40 weeks. No restrictions were placed on dose or language of publication. The reference lists of recently published systematic reviews (ie 2015 to present) were screened for potentially eligible studies.

The four outcomes of interest were as follows: the number of study participants diagnosed with study-emergent epithelial cancer (primary outcome), the number of participants diagnosed with study-emergent epithelial cancers by organ system and histological type, as well as the number of participants whose current solid epithelial cancer progressed during the study treatment period (secondary outcomes). Note that studies were not screened for eligibility based on the outcomes they reported.

2.3 | Study selection

Study screening and selection of published literature and clinical trial registry records were facilitated using DistillerSR, an online systematic review program (Evidence Partners Inc), and a standardized study eligibility checklist. First, two pairs of reviewers (CS and CZ or AJ and CZ) independently screened the titles and abstracts of all de-duplicated records retrieved from the literature search to identify potentially eligible records (eligibility screening level one). Next, the full text (or online clinical trial registry details) of all records considered potentially relevant from level one was independently screened for eligibility by the same two reviewer pairs (screening level two). Discrepancies were resolved through discussion until a consensus was reached.

If no included published study was linked to an eligible grey literature record, it was counted as a unique study. To determine the eligibility of records written in a foreign language, a member of the review team fluent in the language of the document translated its abstract or full text. Google Translate was used to translate foreign-language articles that could not be translated by a member of the review team.²⁶ US FDA and Health Canada clinical reviews and regulatory reports were independently reviewed for inclusion by two authors (CS and CZ) who screened their full text, tables, and figures for potentially relevant studies and data. Again, all discrepancies were resolved through discussion until a consensus was reached.

2.4 | Data extraction

One reviewer (CS or CZ) extracted study data, which were independently verified for accuracy and completeness by another reviewer (AJ, CS or CZ). General study characteristics, such as publication year, location of conduct, treatment duration and funding source, were extracted from all included studies. The patient characteristics (eg mean age, sex, asthma severity, disease duration) and outcome data were also extracted from studies that reported on study-emergent solid epithelial cancer. In this manuscript, we report on the result of these studies. When identified, companion articles and other supporting documents (eg online supplements) were linked with their primary publication. When studies had multiple associated publications, reviewers extracted the most recently adjudicated data for each outcome.

We did not assume that 'zero' cancer events occurred in studies that did not explicitly report on cancer. When the number of participants experiencing an event was not available, the total number of events was extracted; however, these data were not combined in any analysis. Authors were not contacted in the event of missing information.

2.5 | Quality assessment

Two pairs of reviewers (CS and CZ or AJ and CZ) independently assessed the quality of all studies that reported on solid epithelial cancer. Discrepancies were resolved through discussion until a consensus was reached. RCTs were appraised using the Cochrane Risk of Bias (ROB) tool,²⁷ the only included comparative observational study was assessed using the Newcastle-Ottawa Scale (NOS),²⁸ and The Joanna Briggs Institute (JBI) checklist for prevalence studies was used to appraise the quality of all non-comparative observational studies.²⁹ Further details about the methodology used to carry out each type of quality assessment, including the criteria for assessing 'overall' study quality, are provided in Appendix S5.

2.6 | Synthesis of results

Four primary (base-case) analyses were planned: one for each of the outcomes of interest. Before analyses were conducted, we compared studies with available data to identify obvious sources of between-study heterogeneity. Clinical diversity was assessed by comparing baseline data on study participants, as well as interventions and comparators. Methodological diversity was assessed by comparing study designs and the results of study-specific quality and ROB assessments. Any study determined to have been too clinically or methodologically different from the others was analysed separately. Heterogeneity was also examined using the I^2 statistic and a visual inspection of forest plots. We interpreted I^2 values of between 75% and 100% as possibly representing a considerable amount of heterogeneity.³⁰ When there was an inconsistent observed effect across studies (ie $I^2 > 50\%$), the results were explored to determine whether

a clinical or methodological feature explained the differences. If feasible, results were to be analysed by subgroup or meta-regression.

For each outcome, separate meta-analyses were conducted for RCTs and observational studies. Data from single- and two-group cohort studies were also analysed separately. To summarize relative measures of effect, we calculated pooled odds ratios (ORs) and their corresponding 95% confidence intervals using a random-effects model, assuming between-study heterogeneity. When events were rare, however, we calculated Peto odds ratios (pORs) and corresponding 95% confidence intervals.^{31,32} We used the Freeman-Tukey double arcsine transformation^{33,34} to estimate the pooled proportions (and corresponding 95% confidence interval) of study-emergent cancer events in participants of single-group cohort studies. This transformation method allows for the inclusion of studies with one effect measure (ie no comparator from which a relative measure of effect can be calculated) and 'zero' events and helped stabilize the variance of estimates.³⁵ A sensitivity analysis was conducted using the inverse-variance method. Again, a random-effects model was used, assuming between-study heterogeneity.

Data were included for analysis regardless of treatment duration; however, all studies involved participants who received long-term treatment with omalizumab. All meta-analyses were conducted using Comprehensive Meta-Analysis software (version 2; Biostat) and MedCalc software (version 18.2.1). Forest plot summary figures

were created using Microsoft Excel and Word 2007 (Microsoft Corporation). When a meta-analysis was not possible, either because unexplained heterogeneity was substantial (eg $I^2 > 75\%$) or fewer than two studies of similar design reported data, results were summarized descriptively.

2.7 | Reporting biases

Formal assessments for the presence of small-study and publication biases were planned for each outcome using tests for funnel plot asymmetry and associated bias indicators (eg Egger's and Begg's tests).³⁶ These tests, however, were not performed due to an insufficient number of included studies (ie <10) reporting data.³⁶ We addressed publication bias informally by including data from both published and unpublished sources. Language bias was also addressed by including all languages in our search strategy and translating all potentially relevant records written in a foreign language to English during the literature screening process. RCTs were assessed for selective outcome reporting bias using the Cochrane ROB tool.

2.8 | Additional analyses

Five subgroup analyses based on age, sex, length of omalizumab use, history of malignancy and history of autoimmunity were planned;

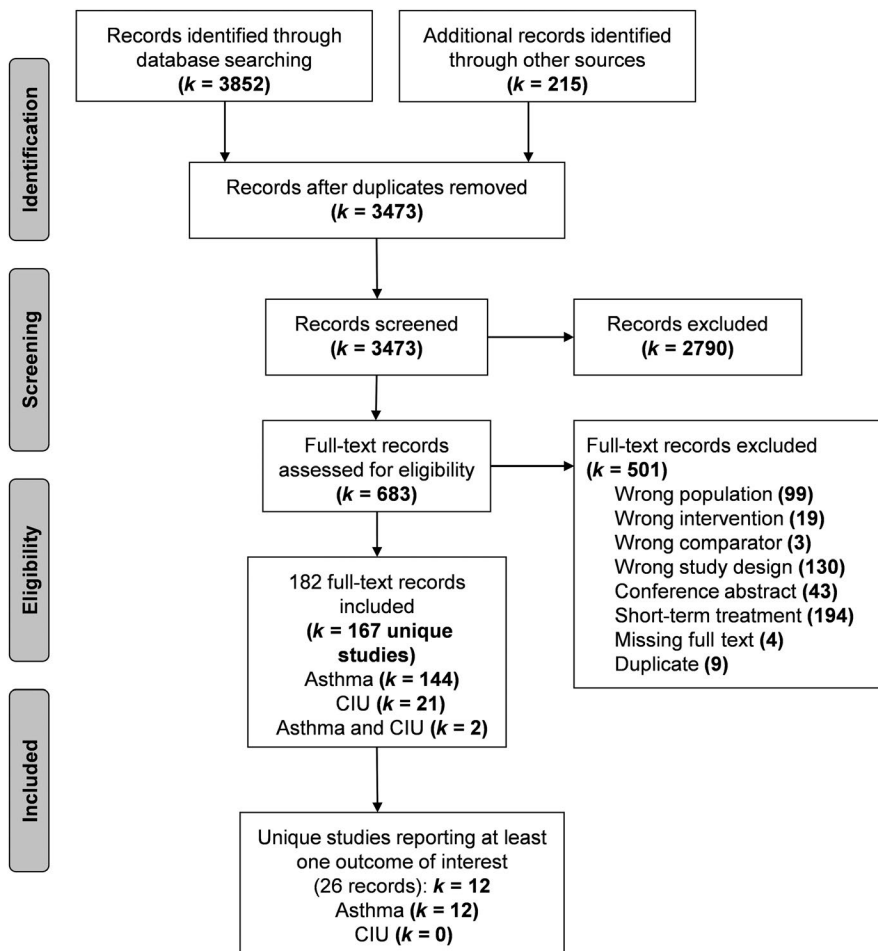


FIGURE 1 Preferred reporting items for systematic reviews and meta-analyses (PRISMA) flow diagram

however, they were not conducted due to a lack of available data. Sensitivity analyses were also planned to assess the influence of study quality (eg low versus high or unclear ROB) and other variables (eg various aspects of the PICO) on the robustness of results. However, due to a lack of available data, these analyses were also not conducted.

3 | RESULTS

As summarized in Figure 1, a total of 4067 records were retrieved through searches of bibliographic databases and grey literature sources. After the removal of duplicates, the titles and abstracts of 3473 records were screened for eligibility. Of the 683 records assessed for eligibility at full text, 182 (representing 167 unique studies) were included in the systematic review. Most studies ($k = 144$, 86%) involved participants with atopic asthma only, 21 (13%) involved participants with CIU, and two studies (1.2%) included participants with either asthma or CIU. Only twelve studies (reported in 26 records) reported on at least one outcome of interest, all of which involved participants with atopic asthma. Appendix S6 provides a list of all included parent ($k = 167$) and associated companion ($k = 15$) publications, and all included grey literature records ($k = 39$ unique studies and four companion records). A list of records excluded after full-text review is available from the authors upon request.

3.1 | Study characteristics

General characteristics of the twelve included studies that reported on study-emergent solid epithelial cancer^{22,37-47} are summarized in Tables 1 and 2. Additional details can be found in Appendix S7. Collectively, these studies included a total of 11 758 participants and encompassed three study types. Three were RCTs,⁴³⁻⁴⁵ one was a comparative observational study (prospective cohort),²² and eight were non-comparative observational studies.^{37-42,46,47} Their publication dates ranged from 2002 to 2018; however, 75% were published in the last 5 years. All studies were published in English.

3.1.1 | Randomized controlled trials

All RCTs that reported on study-emergent solid epithelial cancer⁴³⁻⁴⁵ were funded by Genentech Inc and Novartis Pharmaceuticals. The two-armed XPORT trial by Ledford et al⁴⁵ compared omalizumab discontinuation with dose reduction of concomitant treatment to dose reduction of concomitant treatment alone. A variety of concomitant treatments were allowed (Table 2), and study participants who experienced at least one asthma exacerbation were immediately unblinded and permitted to switch to treatment with omalizumab. Most XPORT participants were recruited from EXCELS,²² a prospective observational study that was also included in this review.

The 2011 trial by Hanania et al (EXTRA)⁴⁴ did not allow participants to switch treatment arms; however, no information on treatment switching was available for the RCT by Buhl et al⁴³ Both of

these studies included a run-in period prior to participant randomization. The trial by Buhl et al⁴³ had two phases during randomization: a phase with stable concomitant treatment followed by a phase with dose reduction of concomitant treatment to the lowest effective dose. A double-blind extension phase followed in the post-randomization period. Trial participants were allowed several types of concomitant standard-of-care treatments (Table 2); however, patients were excluded if they used oral corticosteroids on a regular basis. In the EXTRA trial,⁴⁴ concomitant treatments remained stable post-randomization.

3.1.2 | Observational studies

The EXCELS study by Long et al²² was the only included comparative observational study that reported on study-emergent solid epithelial cancer. This 2014 prospective cohort study, funded by Genentech Inc and Novartis Pharmaceuticals, had one of the longest treatment periods of any included study (median treatment length 36.6 months) and reported results after 5 years. Originally, only patients with no history of, or current, cancer were eligible to take part in EXCELS. However, a protocol amendment was made after more than half (56%) of patients had been recruited, allowing patients with a history of cancer or current cancer to enrol.

Eight other observational studies^{37-42,46,47} were non-comparative longitudinal studies that evaluated outcomes in a group of participants sampled on the basis of a single exposure (ie all subjects received omalizumab). Four studies (67%)^{37-39,42} were prospective, two were registry studies,^{37,40} and five^{39-42,46} were completed at a single centre. One study was funded by Novartis Pharmaceuticals,⁴⁷ two studies^{37,38} were funded by both Genentech Inc and Novartis Pharmaceuticals, three declared no funding,^{39,40,46} and the others^{41,42} did not report on study funding.

3.2 | Participant characteristics

Baseline participant characteristics are summarized in Table 1. Most study participants were women (percentage [range]: 67% [36% to 88%]) and of Caucasian race (84% [70% to 95%]). Collectively, participant mean age and weight [range] were 49 [41 to 69] years and 80 [67 to 87] kg, respectively. Their mean duration of asthma was 24 (range: 19 to 36) years, and mean [range] FEV1 per cent predicted value was 66 [52 to 79] (moderate asthma).

3.2.1 | Randomized controlled trials

The trials by Buhl,⁴³ Hanania⁴⁴ and colleagues were similar in terms of participant characteristics and overall study design as well as intent. Specifically, participants of these two trials were naïve to omalizumab at study entry and were randomized to either begin long-term treatment with omalizumab or continue treatment with standard of care. Their general aim was to evaluate the safety and efficacy of long-term treatment with omalizumab in a controlled setting. In contrast, all participants of the XPORT trial⁴⁵ were already

TABLE 1 Study and participant characteristics

Study	Treatment duration	Location of conduct	Eligible asthma severity	Treatment groups (N)	Age (y), mean (SD), range	Female, n (%)	Disease duration (y), mean (SD), range	FEV ₁ % predicted, mean (SD)
Randomized controlled trials								
Ledford (2017), XPORT ⁴⁵	48 wk	United States (multi-centre)	Moderate or severe	Omalizumab (88) Omalizumab discontinuation (88)	51.1 (11.7) 51.9 (13.3)	63 (71.6) 60 (68.2)	27.3 (17.1) 27.7 (16.1)	75.5 (18.8) 77.7 (19.2)
Hanania (2011), EXTRA ⁴⁴	48 wk	United States & Canada (multi-centre)	Severe	Omalizumab (427) Standard care: ICS and LABA (423)	43.7 (14.3) 45.3 (13.9)	262 (61.4) 295 (70.1)	22.8 (15.4) 24.7 (15.8)	65.4 (15.2) 64.4 (13.9)
Buhl (2002) ⁴³	28 wk + 24 wk extension	Multi-centre (locations NR)	Moderate or severe	Omalizumab (274; 254 in extension) Standard care: Placebo of omalizumab, ICS, SABA (272; 229 in extension)	41, 12-76 40, 13-72	124 (48.8) 120 (52.4)	21, 2-68 19, 1-63	70.0, 32-112 70.4, 22-109
Comparative observational study								
Long (2014), EXCELS ²²	Median (range): 36.6 (0-73) mo	United States (multi-centre)	Moderate or severe	Omalizumab (5007) Standard care (2829)	44 (17) 46 (17)	3199 (63.9) 1880 (66.5)	Both groups: 22	77 (27) 81 (51)
Non-comparative observational studies								
Al-Ahmad (2018) ⁴⁶	1-10 y ^a	Kuwait (single centre)	Moderate or severe	Omalizumab (35)	Ongoing: 41.4 (9.0) ^b Dropouts: 51.9 (16.4) ^b	26 (74.3)	NR	NR
Yorgancıoğlu (2018) ⁴⁷	Minimum 16 wk to 5 y ^c	Turkey (multi-centre)	Severe	Omalizumab (465) ^d	47.7 (11.9), 18-82 ^e	353 (75.9) ^e	Median: 13 IQR (1-48) ^e	61.2 (18.6) ^e
Chippis (2017), PROSPERO ³⁸	12 mo	United States (multi-centre)	Mild, moderate or severe	Omalizumab (806)	47.3 (17.4)	512 (63.5)	24.8 (20.7)	75.4 (20.6)
Tat (2016) ⁴¹	Mean (SD), range: 35.6 (17.8), 9-66 mo	Turkey (single centre)	Severe	Omalizumab (19)	69.3 (5.8)	14 (73.6)	19.4 (8.6)	54.8 (20.8)
Gouder (2015) ³⁹	52 wk	Malta (single centre)	Severe	Omalizumab (22)	52.7 (11)	8 (36)	NR	66.3 (22.9)
Vieira (2014) ⁴²	NR	Portugal (single centre)	Severe	Omalizumab (15)	46.5 (10.8)	13 (86.7)	36.3 (10.8)	51.7 (12.3)
Braunstahl (2013), eXpeRience ³⁷	2 y	International ^f	Moderate or severe	Omalizumab (943)	45 (15.0)	600 (64.9)	19.4 (13.6)	NR

(Continues)

TABLE 1 (Continued)

Study	Treatment duration	Location of conduct	Eligible asthma severity	Treatment groups (N)	Age (y), mean (SD), range	Female, n (%)	Disease duration (y), mean (SD), range	FEV ₁ % predicted, mean (SD)
Mansur (2017) ⁴⁰	Mean (SD), range: 60.7 (30.9), 23–121 mo	United Kingdom (single centre)	Severe	Omalizumab (45)	44.9 (12.7)	37 (81)	NR	61.1 (19.9)

Abbreviations: FEV₁, forced expiratory volume in 1 second; ICS, inhaled corticosteroid; LABA, long-acting beta-agonist; LAMA, long-acting muscarinic antagonists; LTRA, leukotriene receptor antagonist; NA, not applicable; no., number; NR, not reported; OCS, oral corticosteroid; pts, patients; SABA, short-acting beta-agonist; SD, standard deviation.

^aNo summary statistics were provided for treatment duration. The study followed 35 patients who initiated omalizumab in 2008 until 2017, where all patients had at least 1 y of treatment. At 10 y, 20 (57.1%) remained on treatment and 15 discontinued (42.8%).

^bDropouts = patients who stopped treatment with omalizumab at different time-points until the last assessment in 2017; ongoing = patients who continued treatment with omalizumab after the 2017 assessment.

^cNo summary statistics were provided for treatment duration; however, 318/465 (68.4%) participants completed at least 1 y of omalizumab treatment.

^d465 participants were included in the study; however, only 318 (68%) completed at least 1 y of treatment. The reported outcome was reported in an individual who been treated with omalizumab for at least 1 y.

^eBaseline demographics for the entire population, including 109 participants who did not complete 1 y of treatment with omalizumab.

^fArgentina; Bulgaria; Canada; Cyprus; Czech Republic; Hungary; The Netherlands; Philippines; Portugal; Russia; Slovakia; Slovenia; Spain; Taiwan.

on treatment with omalizumab at study entry and the researchers' aim was to evaluate participant response to either continuation, or withdrawal, from long-term treatment.

Participant inclusion in the EXTRA⁴⁴ trial was limited to those with severe allergic asthma, whereas the two other trials (XPORT⁴⁵ and Buhl et al⁴³) included patients with moderate or severe asthma. The ratio of women to men was nearly balanced for the study by Buhl et al⁴³; however, approximately two-thirds of participants in the XPORT⁴⁵ and EXTRA⁴⁴ trials were female. Across RCTs, participants were generally middle-aged (range: 40.5 to 51.5 years), and most were of Caucasian race (range: 74% to 92%). As expected, the baseline characteristics of treatment groups were generally well balanced within each RCT, with the exception of smoking status in the XPORT trial⁴⁵ by Ledford et al. Whereas more than one-third (36.8%) of participants assigned to omalizumab discontinuation were previous smokers, less than one-fifth (18.8%) of those assigned to continue treatment with omalizumab had previously smoked.

3.2.2 | Observational studies

In the EXCELS study,²² baseline characteristics, such as cancer and smoking status, mean BMI and age, were generally well balanced between treatment groups with the exception of a few notable differences. Specifically, 49.6% of the omalizumab-treated cohort had severe asthma compared to only 22.6% of those on standard of care. Furthermore, the median baseline IgE levels in those treated with omalizumab were nearly double that of the cohort treated with standard of care (202 IU/mL vs 108 IU/mL, respectively), and daily use of asthma controller and quick-relief medications also differed between the two treatment groups (22.4% of omalizumab-treated participants used quick-relief medications on a daily basis compared to 14.9% of those treated with other medications).

Participants included in non-comparative studies^{37-42,46,47} varied with respect to a variety of baseline characteristics. For example, five studies^{39-42,47} recruited patients with severe asthma only, while the other three^{37,38,46} included patients with moderate or severe asthma. One of these studies³⁸ also enrolled participants with mild asthma, though the FEV₁ per cent predicted values reported at baseline indicate that, on average, participants had moderate asthma (mean [SD]: 75.4 [20.6]). Only older adults (≥65 years) were eligible to participate in the study by Tat et al,⁴¹ whereas the other seven studies^{37-40,42,46,47} included participants who were generally middle-aged. Only eight of 22 participants (36%) in the study by Gouder et al³⁹ were women; a much lower proportion than all other included studies. In two studies,^{37,39} nearly all individuals were reported to be of Caucasian race; however, this type of information was not reported in the other six studies.^{38,40-42,46,47} There was also some variation in the baseline weight of participants. Specifically, the study by Vieira et al⁴² included participants with the lowest mean [SD] weight (66.8 [10.6] kg), while PROSPERO³⁸ and the study by Mansur et al⁴⁰ involved participants with the highest mean [SD] weights (85.4 [24.2] kg and 85.9 [21.5] kg, respectively). The mean (SD) weight

TABLE 2 Summary of study-emergent solid epithelial cancer by organ system affected and histological type (RCTs)

Author (y). Study name	Study duration	Permitted concomitant/standard care asthma medications	Total # participants with any solid epithelial tumour ^a , %	Organ system affected	Cancer histology
Omalizumab-experienced participants					
Ledford et al (2017), XPORT ⁴⁵	48 wk	ICS, LABA, LTRA, OCS, theophylline, 5-lipoxygenase inhibitors, anticholinergics (oral, inhaled and/or nasal), mast cell stabilizers	Omalizumab continuation: 1/88, 1.1% Placebo (omalizumab discontinuation): 1/88, 1.1%	Digestive: colon Reproductive [female]: Organ unspecified	Adenocarcinoma Mixed Müllerian tumour
Omalizumab-naïve participants					
Hanania et al (2011), EXTRA ⁴⁴	48 wk	ICS, LABA, LTRA, OCS, SABA, theophylline, zileuton, anticholinergics (oral, inhaled or nasal)	Omalizumab: 1/428 ^b , 0.2% Standard care: 3/420 ^c , 0.7%	Not reported Digestive: Colon; stomach; oesophagus	Not reported
Buhl et al (2002) ⁴³	52 wk ^e	ICS, LABA, LTRA, OCS (for asthma exacerbations), SABA, xanthines (eg theophylline)	Omalizumab: 1/254 ^d , 0.4% Standard care: 0/229 ^d , 0%	Reproductive [male]: Prostate Not applicable	Not reported

Abbreviations: ICS, inhaled corticosteroid; LABA, long-acting beta-agonist; LTRA, leukotriene receptor antagonist; NR, not reported; OCS, oral corticosteroid; OMA, omalizumab; RCT, randomized controlled trial; SABA, short-acting beta-agonist.

^aNumerator = # participants with an event; denominator = # of participants included in the safety analysis.

^bn = 427 participants were randomized; however, one patient in the standard care arm received at least one dose of omalizumab and was analysed in the omalizumab arm for safety outcomes.

^cTwo participants did not receive OMA and were excluded from the safety analysis.

^dAnalysis was based only on 254/274 and 229/272 participants treated with omalizumab or standard care, respectively, who entered the double-blind extension phase.

^e28-wk trial + 24-wk double-blind extension period.

of participants included in the other four non-comparative cohort studies^{37,41,46,47} fell between these values.

3.3 | Quality assessment

A complete set of judgements for each study's ROB assessment are provided in Table S8a. Briefly, ROB varied widely across the three included RCTs that reported on solid epithelial cancer.⁴³⁻⁴⁵ Only the EXTRA⁴⁴ trial by Hanania et al was judged to be of 'low' overall ROB as it was assessed low ROB ratings for all key domains (see Appendix S5 for details). Because the trial by Buhl et al⁴³ was assessed a 'high' ROB rating in at least one key domain, it was judged to be 'high' in overall ROB. At least one key ROB domain was assessed an 'unclear' ROB rating for the XPORT trial by Ledford et al,⁴⁵ which led to it being assessed an overall judgement of 'unclear' ROB.

Among observational studies reporting on the outcome of interest, the prospective cohort study by Long et al²² was judged to be of 'fair' overall quality based on the thresholds for converting the NOS scores to AHRQ quality standards (see Tables S5a and S8b). The evidence yielded by all non-comparative cohort studies³⁷⁻⁴² was considered to be of 'low' quality. Nonetheless, more than two-thirds (71%) of the JBI checklist items were adequately addressed across the eight studies assessed (see Figure S8a).

3.4 | Synthesis of results

3.4.1 | Randomized controlled trials

As shown in Table 2, across RCTs, the number of participants reporting at least one study-emergent solid epithelial cancer event was low. Two (0.3%) participants assigned to begin treatment with omalizumab after study entry were diagnosed with at least one study-emergent solid epithelial tumour compared to three (0.5%) participants assigned to continue treatment with standard of care. Among omalizumab-experienced individuals (see Ledford et al⁴⁵ in Table 2), the proportion of participants diagnosed with any type of study-emergent solid epithelial tumour was not different between study groups (1.1% of participants each assigned to either continue or discontinue omalizumab).

Due to previously described clinical and methodological differences, only data from two^{43,44} of the three⁴³⁻⁴⁵ included RCTs reporting on solid epithelial cancer were combined to generate a pooled effect estimate of the effect that prolonged treatment with omalizumab has on the incidence of solid epithelial cancer in patients with atopic asthma (Figure 2). Overall, the pooled pOR was 0.65 and was not statistically significant (95% CI: 0.11, 3.74, $I^2 = 41\%$).

Results from the XPORT trial⁴⁵ (not shown in Figure 2) demonstrated no significant difference in the odds of developing cancer between participants who continued, compared to those who discontinued, treatment with omalizumab (OR = 1.00 [95% CI: 0.06, 16.12]).

All solid epithelial cancers reported by RCTs affected organs of the digestive and reproductive systems. Only one study⁴⁵ specified

TABLE 3 Summary of study-emergent solid epithelial cancer by organ system affected and histological type (observational studies)

Author (y), Study name	Study duration	Permitted concomitant/ standard care asthma medications	Total # participants with any solid epithelial tumour ^a , %	Organ system affected [histological type] ^b						
				Integumentary	Respiratory	Reproductive (male)	Digestive	Endocrine	Urinary	Reproductive (female)
Comparative observational study										
Long et al (2014), EXCELS ^{22c}	Median, range: 36.6, 0-73 mo	Daily use of controller and quick-relief medications	Omalizumab: 114/5 007; 2.3%	Breast: 29/3 199; 0.9%	Lung: 6/5 007; 0.1%	Prostate: 17/1 808; 0.9%	Colorectal: 14/5 007; 0.3%	Thyroid: 7/5 007; 0.1%	-	-
			Standard care: 63/2 829; 2.2%	Breast: 13/1 880; 0.7%	Lung: 7/2 829; 0.2%	Prostate: 5/949; 0.5%	Colorectal: 3/2 829; 0.1%	Thyroid: 1/2 829; 0.04%	-	-
Non-comparative observational studies										
Al-Ahmad et al (2018) ⁴⁶	1-10 y ^d	NR	Omalizumab: 0/35; 0%	0/35; 0%	0/35; 0%	0/9; 0%	0/35; 0%	0/35; 0%	0/35; 0%	0/26; 0%
Yorgancıoğlu et al (2018)	Minimum 16 wk to 5 y ^e	ICS, LABA, LTRA (some patients)	Omalizumab: 1/318 ^f ; 1.3%	-	-	Prostate: 1/77; 1.3%	-	-	-	-
Chippis et al (2017), PROSPERO ³⁸	12 mo	ICS, LABA, SABA, LTRA, OCS, anticholinergics such as tiotropium (some patients)	Omalizumab: 5/801 ^g ; 0.5%	Breast: 1/512; 0.2%	-	Prostate: 1/289; 0.3%	-	Thyroid: 1/801; 0.1%	Kidney: [renal cell carcinoma] 1/801; 0.1%	Ovarian: 1/512; 0.2%
Tat et al (2016) ⁴¹	Mean (SD), range: 35.6 (17.8), 9-66 mo	ICS, LABA, LTRA	Omalizumab: 1/19; 5.3%	-	Lung (bronchial) 1/19; 5.3%	-	-	-	-	-
Vieira et al (2014) ⁴²	12 mo ^h	Physicians could prescribe, withdraw or change dose of any approved asthma medication (including omalizumab) for best control	Omalizumab: 1/15; 6.7%	Breast: 1/13; 7.7%	-	-	-	-	-	-
Braunstaht et al (2013), eXperience ³⁷	24 mo	ICS, LABA, SABA, LTRA, OCS, LAMA	Omalizumab: 1/925 ⁱ ; 0.1%	-	Lung: 1/925; 0.1%	-	-	-	-	-

(Continues)

TABLE 1 (Continued)

Author (y), Study name	Study duration	Permitted concomitant/ standard care asthma medications	Total # participants with any solid epithelial tumour ^a , %	Organ system affected [histological type] ^b						
				Integumentary	Respiratory	Reproductive (male)	Digestive	Endocrine	Urinary	Reproductive (female)
Mansur et al (2017) ⁴⁰	Mean (SD), range: 60.7 (30.9), 23-121 mo	ICS, OCS (stopped receiving or dose reduced during study)	Omalizumab: 2/45; 4.4%	Breast: 1/37; 2.7% Skin [basal cell carcinoma] 1/45; 2.2%	-	-	-	-	-	-
Gouder et al (2015) ³⁹	12 mo	ICS, LABA, LTRA, OCS, theophylline	Omalizumab: 0/22; 0%	0/22; 0%	0/22; 0%	0/14; 0%	0/22; 0%	0/22; 0%	0/22; 0%	0/8; 0%

Abbreviations: ICS, inhaled corticosteroid; LABA, long-acting beta-agonist; LAMA, long-acting muscarinic antagonists; LTRA, leukotriene receptor antagonist; NA, not applicable; no., number; NR, not reported; OCS, oral corticosteroid; pts, patients; SABA, short-acting beta-agonist; SD, standard deviation.

^aNumerator = # participants with an event; denominator = # of participants included in the safety analysis. Data from Long et al (EXCELS) study are as follows: number of cancer events/ number of participants at risk who received treatment. The denominator for breast cancer includes women only as male breast cancer is rare, accounting for only ~1% of all cases.⁵⁸

^bNumerator = # participants with an event; denominator = # participants included in the safety analysis. Data from Long et al (EXCELS) study are as follows: number of cancer events/ number of participants at risk who received treatment. The denominator for breast cancer includes women only as male breast cancer is rare, accounting for only ~1% of all cases.⁵⁸

^cThis study excluded non-melanoma skin cancer and did not clearly report if any cases were in other organ systems (based on organ-specific reporting).

^dNo summary statistics were provided for treatment duration. The study followed 35 patients who initiated omalizumab in 2008 until 2017, where all patients had at least 1 y of treatment. At 10 y, 20 (57.1%) remained on treatment and 15 discontinued (42.8%).

^eNo summary statistics were provided for treatment duration; however, 318/465 (68.4%) participants completed at least 1 y of omalizumab treatment.

^fThe number of men who completed 1 y of treatment was not reported by the authors. We estimated this denominator by assuming that the ratio of men: women after 1 y of treatment was consistent with the proportion of men: women at study baseline (ie 24.1% of 318 participants were men).

^gA total of 806 participants were enrolled; only 801 were included in the safety analysis of serious adverse events reported on ClinicalTrials.gov (NCT01922037)

^h14 patients completed 12 mo of treatment; 10 patients completed 24 mo and 4 completed 36 mo of treatment with omalizumab.

ⁱA total of 943 participants were enrolled; only 925 were included in the safety analysis, which included 'all enrolled patients who received at least one dose of omalizumab and had at least one post-baseline effectiveness assessment'.

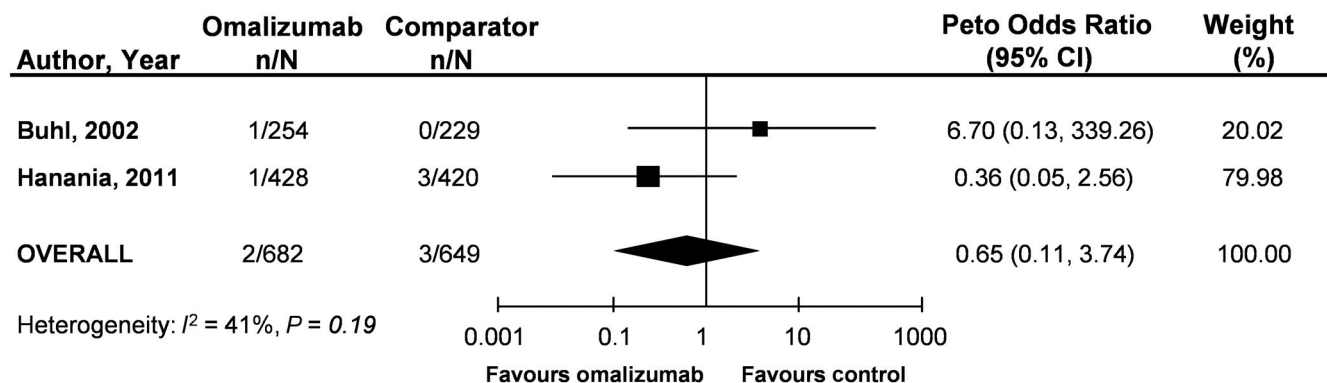


FIGURE 2 Forest plot of all study-emergent solid epithelial cancer events reported by RCTs

the histological type (secondary outcome, see Table 2). Two omalizumab-experienced participants in the XPORT trial⁴⁵ were diagnosed with a solid tumour during the study's 48-week treatment period: one participant was assigned to continue treatment with omalizumab (colon adenocarcinoma) and the other participant, assigned to discontinue treatment with omalizumab, was diagnosed with a mixed Müllerian tumour (organ unspecified). Among participants who were omalizumab-naïve prior to study entry, three (0.7%) who received standard care in the EXTRA trial⁴⁴ were diagnosed with digestive organ tumours (colon, stomach, oesophagus). Among EXTRA participants assigned to 48 weeks of treatment with omalizumab, only one (0.2%) was diagnosed with a solid tumour. The authors did not report details about histological type or the organ system affected.

3.4.2 | Observational studies

Nine included observational studies^{22,37-42,46,47} reported on study-emergent solid epithelial cancer (Table 3). Whereas the authors of the prospective cohort EXCELS²² reported on the total number of study-emergent cancer events in each treatment group during the study period, the authors of each non-comparative observational study^{37-42,46,47} reported on the number of participants who developed a solid epithelial tumour during the study period. As such, the findings of EXCELS²² are reported separately from those of the non-comparative studies.

Long et al²² reported 114 and 63 incident solid epithelial cancer events in participants treated with either long-term omalizumab or standard of care, respectively. While the number of study-emergent epithelial cancers was numerically higher in participants treated with omalizumab, when the number of cancer events is expressed as a percentage of all participants who received treatment (ie assuming one cancer event per participant treated), the ratios of cancer events are nearly identical (2.3% vs 2.2%).

Across non-comparative observational studies,^{37-42,46,47} the percentage of participants diagnosed with any type of solid epithelial cancer during the study period ranged from 0%^{39,46} to 6.67%.⁴² As illustrated in Figure 3, the meta-proportion of participants diagnosed with solid epithelial cancer was low at 0.86% (95% CI: 0.24, 1.86%).

All solid epithelial cancers reported across observational studies affected at least one of six different organ systems (Table 3). Digestive cancer was reported in participants of EXCELS²² (colorectal), and cancer of the endocrine system (thyroid) was reported in participants of both EXCELS²² and PROSPERO.³⁸ Four observational studies^{22,38,40,42} reported at least one study-emergent breast cancer. Only PROSPERO³⁸ reported a single case each of urinary (kidney) cancer and cancer of the female reproductive system (ovarian). The studies by Chipps³⁸ and Mansur et al⁴⁰ were the only observational studies to report cancer by histological type (renal³⁸ and basal cell⁴⁰ carcinoma).

3.5 | Additional analyses

Subgroup analyses could not be conducted because too few studies reported outcomes by any subgroup of interest (ie age, sex, length of omalizumab use, history of malignancy and history of autoimmunity). Likewise, we did not conduct sensitivity analyses as planned because the available evidence was too limited to perform any robust analysis.

4 | DISCUSSION

We identified a total of 167 unique randomized, quasi-randomized, controlled clinical trials and observational studies that involved participants (≥ 12 years) with moderate-to-severe persistent asthma or CIU who received long-term treatment with omalizumab. Only twelve (7.2%) included studies reported on study-emergent solid epithelial tumours, none of which involved participants with CIU. In general, the overall quality of these studies was low.

4.1 | Randomized controlled trials

Our MA of RCTs showed no statistically significant difference in the odds of cancer between participants treated with omalizumab compared to those treated with standard of care. We hesitate, however, to draw any firm conclusions from this finding for a variety of reasons. First, only data from two RCTs^{43,44} were included

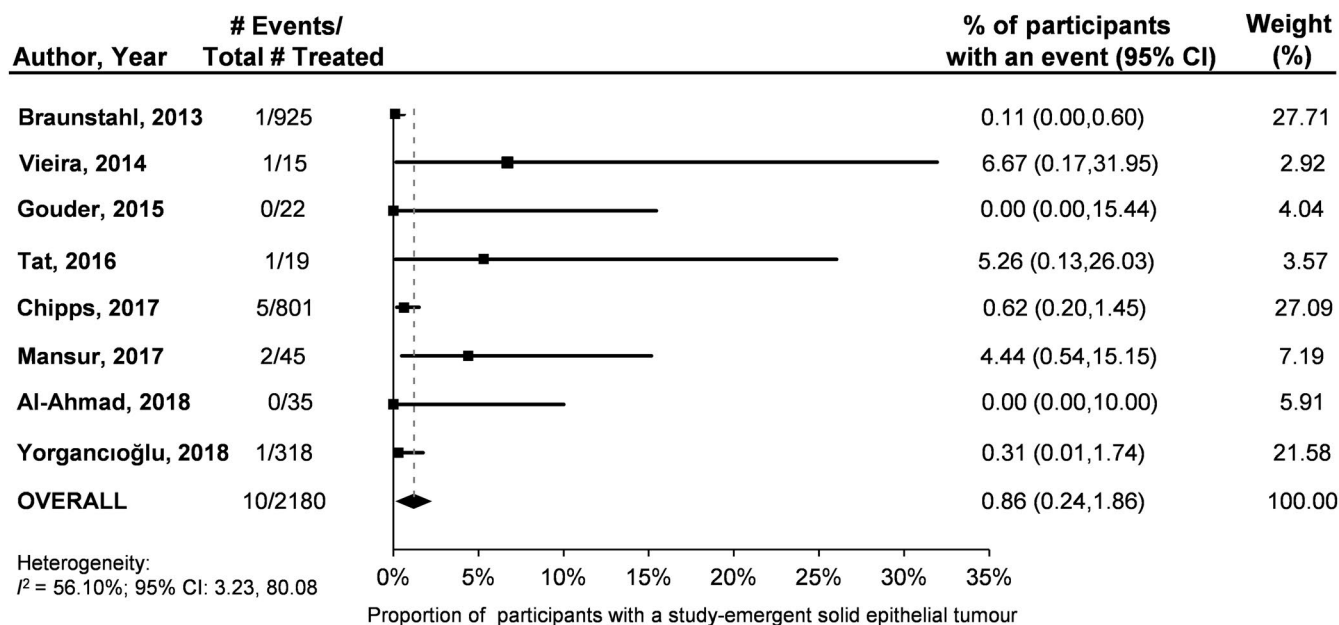


FIGURE 3 Forest plot of all study-emergent solid epithelial cancer events reported by non-comparative observational studies

in the MA. While each study's sample size was relatively large ($N = 483^{43}$ and $N = 848^{44}$), they may not have been adequately powered to detect an association between treatment with omalizumab and incidence of solid epithelial cancer even if one exists. Furthermore, the minimum latency period of these types of malignancies has been estimated at 4 years;⁴⁸ thus, a treatment period of approximately 1 year may not have been sufficient to accurately detect study-emergent cancer events. Finally, unexplained between-study heterogeneity was moderately high ($I^2 = 41\%$) and, perhaps most importantly, the directions of effect are not consistent between the two RCTs. Specifically, whereas the findings of the study by Buhl et al⁴³ suggest that there was a (non-significant) increase in the odds of study-emergent cancers among participants treated with omalizumab, the findings of the study by Hanania et al⁴⁴ suggest the opposite.

At least two previous reviews have used clinical trial data to evaluate the safety of omalizumab with specific focus on cancer risk.^{49,50} A 2009 review by Corren et al⁴⁹ pooled data from 35 phase I, II and III studies of omalizumab and compared the incidence of malignancy among participants treated with this medication to the 'expected' number of incident cancer events in the general US population (reported in the National Institutes of Health Surveillance, Epidemiology and End-Results (SEER) database).⁴⁹ The authors reported a non-statistically significant standardized incidence ratio of 0.99 (95% CI: 0.55, 1.63) and concluded the data did not support an increased incidence of malignant neoplasms among patients who received omalizumab compared to the 'expected number of events' in the general US population. A more recent (2012) review by Busse et al⁵⁰ that pooled safety data on malignancies from Novartis and Genentech sponsored clinical trials and 'ARGUS' (Novartis' safety and pharmacovigilance database) also concluded that treatment with omalizumab was 'unlikely' to cause malignancy (rate ratio: omalizumab vs placebo, 0.93 [95% CI: 0.39, 2.27]).

Similar to this review, studies included in the reviews published by Corren⁴⁹ and Busse⁵⁰ were not required to have defined malignancy as a pre-specified adverse event of interest. Given that many cancers can grow undetected for several years,⁴⁸ it is possible that some study-emergent tumours went undetected by included studies, especially if researchers were not routinely screening for the disease. Few other similarities exist between these reviews and ours, however, which makes direct comparisons difficult. For example, in the reviews by Corren⁴⁹ and Busse,⁵⁰ malignancy of any kind was of interest (except non-melanoma skin cancer in Busse et al⁵⁰). In contrast, our focus was on study-emergent (or progression of) solid epithelial tumours. Furthermore, the reviews by Busse⁵⁰ and Corren⁴⁹ involved heterogeneous patient populations (ie patients with conditions other than atopic asthma and CIU) and long-term treatment with omalizumab was not a requirement for study inclusion. In Busse et al,⁵⁰ for example, any adverse event was eligible as long as it occurred on or after a patient's first dose of omalizumab. In the review by Corren et al,⁴⁹ only 13% of the study population with allergic asthma received long-term treatment (≥ 52 weeks).

4.2 | Observational studies

In the prospective cohort by Long et al,²² the proportion of study-emergent solid epithelial tumour events was nearly identical in both study groups (omalizumab: 2.3%, standard of care: 2.2%). To compare the number of study-emergent cancer events to those of the general population, Long et al²² calculated a standardized morbidity ratio (SMR) using data from the SEER database. Ultimately, the authors reported no statistically significant difference in incident cancer (excluding non-melanoma skin cancer) between those treated with omalizumab compared to what would be expected in the general US population over a comparable period of time (SMR = 0.91, 95% CI: 0.75-1.09).

Li et al²³ have critiqued the findings of EXCELS,²² highlighting many of its shortcomings to ultimately conclude that the study did not rule out a potential cancer risk among those treated with long-term omalizumab. Patients who were already receiving omalizumab were eligible to participate in EXCELS,²² and cancer history prior to study enrolment was not captured for most participants. Indeed, if there is a causal association between treatment with omalizumab and cancer, treatment-experienced participants that had not developed a malignancy prior to study entry may have been more 'cancer-resilient' than those who were omalizumab-naïve.²³ The study attempted to address this issue with a protocol amendment that allowed individuals with a history of cancer, pre-malignant condition or active cancer to enrol. This amendment; however, required the retrospective collection of information on cancer history from the 56% of participants recruited prior to the amendment.²² What remains unclear is whether or not participants recruited prior to the amendment had a pre-malignant condition that was undetected as the retrospective collection of data would not necessarily have captured this information.

4.3 | Non-comparative observational studies

Data obtained from non-comparative observational studies can help researchers gain insight about medication safety outside of the strictly controlled environment of RCTs through 'real-world' observations;⁵¹ however, these types of studies are of limited value because they lack an unexposed comparison group. As noted by others,^{52,53} to make meaningful inferences about the effects of interventions, single-arm post-marketing studies must compare their results of to a reference group (eg a widely acceptable threshold value).

The authors of the eight included non-comparative studies^{37-42,46,47} reporting on solid epithelial cancer made no reference to a comparable population cancer rate, and we were unable to identify a single, population-based rate of 'solid epithelial cancer' with which to compare our pooled effect estimate of 0.86% (95% CI: 0.24 to 1.86). Further, even if a population-based reference statistic had been identified, a direct comparison would be difficult as the studies were completed in a number of specific countries, across which the incidence of cancer subtypes may vary. For example, the age-standardized incidence rates of the most commonly reported type of epithelial cancer (breast) range from 0.047% (Kuwait in 2012)⁵⁴ to 0.31% (Malta in 2013).⁵⁵ While each of the included studies conducted in those two countries^{39,46} reported zero study-emergent cancer events, meaningful comparisons are difficult as their sample sizes were very low with only $n = 35$ ⁴⁶ and $n = 22$ ³⁹ participants.

4.4 | Strengths and limitations

We conducted a robust SR of scientific literature following established systematic review methodology⁵⁶ that involved explicit eligibility criteria, a comprehensive peer-reviewed literature search strategy and a priori registration of the review protocol. The findings of this study should, however, be viewed in the context of its

limitations, especially with regard to both the quality and the quantity of evidence available for analysis.

Few studies that met our inclusion criteria reported on solid epithelial cancer, which limited our ability to perform meta-analyses, conduct subgroup and sensitivity analyses, and formally test for the presence of publication bias. Indeed, because our 'counts' of cancer events were limited to those explicitly reported in included studies, our analysis had no way of capturing the occurrence of cancer events that were present but not detected (cancer latency period), or the complete non-occurrence of events. Perhaps more importantly, the average omalizumab treatment length of approximately 2 years across all studies may not have been of sufficient length to observe solid epithelial cancer events because these types of malignancies are believed to have a minimum latency period of 4 years, with some types extending well beyond that.⁴⁸

5 | CONCLUSIONS

There is insufficient evidence to determine whether long-term treatment with omalizumab influences the development or progression of solid epithelial cancer in patients with moderate-to-severe persistent allergic asthma. At present, no published data on the incidence of solid epithelial cancer are available for patients with CIU undergoing long-term continuous treatment with omalizumab. This absence of evidence should not be interpreted as clear evidence of no such association. Rather, it highlights the need for additional long-term, adequately powered, comparative studies to be completed on these study populations that are specifically focused on risk of malignancy and cancer recurrence or progression. Given the present uncertainty of evidence on this topic, and the potential for new research to influence policy decisions on the use of omalizumab, the currency of the evidence on this topic should be maintained through a 'living' systematic review.⁵⁷

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CONFLICT OF INTEREST

The authors declare no conflict of interest.

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58. Weiss JR, Moysich KB, Swede H. Epidemiology of male breast cancer. *Cancer Epidemiol Biomarkers Prev*. 2005;14(1):20-26.

SUPPORTING INFORMATION

Additional supporting information may be found online in the Supporting Information section at the end of the article.

How to cite this article: Johnston A, Smith C, Zheng C, et al. Influence of prolonged treatment with omalizumab on the development of solid epithelial cancer in patients with atopic asthma and chronic idiopathic urticaria: A systematic review and meta-analysis. *Clin Exp Allergy*. 2019;49:1291-1305. <https://doi.org/10.1111/cea.13457>

Supplemental Information

Contents

Supplement 1: PRISMA Checklist.....	1
Supplement 2: Initial Literature Search Strategies.....	4
Supplement 3: Updated Literature Search Strategies.....	10
Supplement 4: Study Eligibility Criteria.....	15
Supplement 5: Quality Assessment Methodology.....	17
Supplement 6: List of Included Studies.....	19
Supplement 7: Detailed Study Characteristics.....	31
Supplement 8: Quality Assessment Results	38

List of Supplemental Tables

Table S5 a: Thresholds for Converting NOS Scores to AHRQ Overall Study Quality Standards	18
Table S8 a: Results of the ROB Assessments of Included RCTs Reporting at Least One Outcome.....	38
Table S8 b: Results of the Newcastle-Ottawa Scale Assessment of the Study by Long et al.....	39

List of Supplemental Figures

Figure S8 a: Results of the JBI Checklist for Prevalence Studies Assessment of Eight Non-comparative Cohort Studies.....	40
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Supplement 1: PRISMA Checklist

Section/topic	#	Checklist item	Reported on page #
TITLE			
Title	1	Identify the report as a systematic review, meta-analysis, or both.	Title/abstract
ABSTRACT			
Structured summary	2	Provide a structured summary including, as applicable: background; objectives; data sources; study eligibility criteria, participants, and interventions; study appraisal and synthesis methods; results; limitations; conclusions and implications of key findings; systematic review registration number.	Page 1
INTRODUCTION			
Rationale	3	Describe the rationale for the review in the context of what is already known.	Pages 3-5
Objectives	4	Provide an explicit statement of questions being addressed with reference to participants, interventions, comparisons, outcomes, and study design (PICOS).	Page 6; Supplement 3
METHODS			
Protocol and registration	5	Indicate if a review protocol exists, if and where it can be accessed (e.g., Web address), and, if available, provide registration information including registration number.	Abstract
Eligibility criteria	6	Specify study characteristics (e.g., PICOS, length of follow-up) and report characteristics (e.g., years considered, language, publication status) used as criteria for eligibility, giving rationale.	Page 6; Supplement 3
Information sources	7	Describe all information sources (e.g., databases with dates of coverage, contact with study authors to identify additional studies) in the search and date last searched.	Pages 5-6
Search	8	Present full electronic search strategy for at least one database, including any limits used, such that it could be repeated.	Supplement 2
Study selection	9	State the process for selecting studies (i.e., screening, eligibility, included in systematic review, and, if applicable, included in the meta-analysis).	Pages 6-7
Data collection process	10	Describe method of data extraction from reports (e.g., piloted forms, independently, in duplicate) and any processes for obtaining and confirming data from investigators.	Page 7
Data items	11	List and define all variables for which data were sought (e.g., PICOS, funding sources) and any assumptions and simplifications made.	Page 7

METHODS (cont'd)				
Risk of bias in individual studies	12	Describe methods used for assessing risk of bias of individual studies (including specification of whether this was done at the study or outcome level), and how this information is to be used in any data synthesis.		Page 7-8
Summary measures	13	State the principal summary measures (e.g., risk ratio, difference in means).		Pages 8-9
Synthesis of results	14	Describe the methods of handling data and combining results of studies, if done, including measures of consistency (e.g., I ²) for each meta-analysis.		Pages 8-9
Section/topic	#	Checklist item		Reported on page #
Risk of bias across studies	15	Specify any assessment of risk of bias that may affect the cumulative evidence (e.g., publication bias, selective reporting within studies).		Page 9
Additional analyses	16	Describe methods of additional analyses (e.g., sensitivity or subgroup analyses, meta-regression), if done, indicating which were pre-specified.		Page 9
RESULTS				
Study selection	17	Give numbers of studies screened, assessed for eligibility, and included in the review, with reasons for exclusions at each stage, ideally with a flow diagram.		Page 10, Figure 1
Study characteristics	18	For each study, present characteristics for which data were extracted (e.g., study size, PICOS, follow-up period) and provide the citations.		Table 1
Risk of bias within studies	19	Present data on risk of bias of each study and, if available, any outcome level assessment (see item 12).		Page 14; Supplement 7
Results of individual studies	20	For all outcomes considered (benefits or harms), present, for each study: (a) simple summary data for each intervention group (b) effect estimates and confidence intervals, ideally with a forest plot.		Figures 1, 2
Synthesis of results	21	Present results of each meta-analysis done, including confidence intervals and measures of consistency.		Pages 15-16
Risk of bias across studies	22	Present results of any assessment of risk of bias across studies (see Item 15).		Page 14; Supplement 7
Additional analysis	23	Give results of additional analyses, if done (e.g., sensitivity or subgroup analyses, meta-regression [see Item 16]).		Page 17

DISCUSSION			
Summary of evidence	24	Summarize the main findings including the strength of evidence for each main outcome; consider their relevance to key groups (e.g., healthcare providers, users, and policy makers).	Page 17-20
Limitations	25	Discuss limitations at study and outcome level (e.g., risk of bias), and at review-level (e.g., incomplete retrieval of identified research, reporting bias).	Page 21-22
Conclusions	26	Provide a general interpretation of the results in the context of other evidence, and implications for future research.	Page 22
FUNDING			
Funding	27	Describe sources of funding for the systematic review and other support (e.g., supply of data); role of funders for the systematic review.	

From: Moher D, Liberati A, Tetzlaff J, Altman DG, The PRISMA Group (2009). Preferred Reporting Items for Systematic Reviews and Meta-Analyses: The PRISMA Statement. PLoS Med 6(7): e1000097. doi:10.1371/journal.pmed1000097

For more information, visit: www.prisma-statement.org.

Page 2 of 2

Supplement 2: Initial Literature Search Strategies

Omalizumab
Final Strategies
2017 Nov 23

PRIMARY STUDIES

Ovid Multifile

Database: Embase Classic+Embase <1947 to 2017 November 22>, Ovid MEDLINE(R) ALL <1946 to November 22, 2017>

Search Strategy:

-
- 1 Omalizumab/ (7272)
 - 2 (omalizumab\$2 or xolair\$2).tw,kf. (5625)
 - 3 (HSDB 5742 or HSDB5742 or HSDB 8176 or HSDB8176 or hu 901 or hu901 or rhuMabE25 or rhuMab-E25 or rhu Mab-E25 or rhu MADE25 or UNII-2P471X1Z11).tw,kf. (115)
 - 4 omalizumab.m. (6129)
 - 5 or/1-4 [OMALIZUMAB] (8151)
 - 6 exp Animals/ not (exp Animals/ and Humans/) (15763466)
 - 7 5 not 6 [ANIMAL-ONLY REMOVED] (5032)
 - 8 (controlled clinical trial or randomized controlled trial or pragmatic clinical trial).pt. (600795)
 - 9 clinical trials as topic.sh. (197039)
 - 10 (random#ed or random#ation or randomly or RCT\$1 or placebo*).tw,kf. (2059233)
 - 11 ((singl* or doubl* or trebl* or tripl*) adj (mask* or blind* or dumm*)).tw,kf. (382568)
 - 12 trial.ti. (444068)
 - 13 or/8-12 (2548804)
 - 14 7 and 13 [RCTs] (778)
 - 15 controlled clinical trial.pt. (100426)
 - 16 Controlled Clinical Trial/ or Controlled Clinical Trials as Topic/ (568072)
 - 17 (control* adj2 trial*).tw,kf. (520361)
 - 18 Non-Randomized Controlled Trials as Topic/ (9817)
 - 19 (nonrandom* or non-random* or quasi-random* or quasi-experiment*).tw,kf. (106997)
 - 20 (nRCT or nRCTs or non-RCT?).tw,kf. (1532)
 - 21 Controlled Before-After Studies/ (208500)
 - 22 (control* adj3 ("before and after" or "before after")).tw,kf. (8677)
 - 23 Interrupted Time Series Analysis/ (200439)
 - 24 time series.tw,kf. (52435)
 - 25 (pre- adj3 post-).tw,kf. (181983)
 - 26 (pretest adj3 posttest).tw,kf. (9443)
 - 27 Historically Controlled Study/ (218776)
 - 28 (control* adj2 stud\$3).tw,kf. (483623)
 - 29 Control Groups/ (126446)
 - 30 (control* adj2 group\$1).tw,kf. (1066572)
 - 31 trial.ti. (444068)
 - 32 or/15-31 (3027061)
 - 33 7 and 32 [NON-RCTs] (637)
 - 34 exp Cohort Studies/ (2204054)
 - 35 cohort?.tw,kf. (1207542)
 - 36 Retrospective Studies/ (1094799)
 - 37 (longitudinal or prospective or retrospective).tw,kf. (2643723)
 - 38 ((followup or follow-up) adj (study or studies)).tw,kf. (112651)
 - 39 Observational study.pt. (48871)
 - 40 (observation\$2 adj (study or studies)).tw,kf. (206388)
 - 41 ((population or population-based) adj (study or studies or analys#s)).tw,kf. (36328)
 - 42 ((multidimensional or multi-dimensional) adj (study or studies)).tw,kf. (241)

43 Comparative Study.pt. (1936005)
44 ((comparative or comparison) adj (study or studies)).tw,kf. (237442)
45 exp Case-Control Studies/ (1115081)
46 ((case-control* or case-based or case-comparison) adj (study or studies)).tw,kf. (211529)
47 or/34-46 (6805070)
48 7 and 47 [OBSERVATIONAL STUDIES] (624)
49 14 or 33 or 48 [ALL STUDY DESIGNS] (1431)
50 (comment or editorial or news or newspaper article).pt. (1813729)
51 (letter not (letter and randomized controlled trial)).pt. (2030841)
52 49 not (50 or 51) [OPINION PIECES REMOVED] (1384)
53 52 use emczd (681)
54 52 not 53 [MEDLINE RECORDS] (703)
55 Omalizumab/ (7272)
56 (omalizumab\$2 or xolair\$2).tw,kw. (5722)
57 (HSDB 5742 or HSDB5742 or HSDB 8176 or HSDB8176 or hu 901 or hu901 or rhuMabE25 or rhuMab-E25 or rhu Mab-E25 or rhu MADE25 or UNII-2P471X1Z11).tw,kw. (121)
58 omalizumab.m. (6129)
59 or/55-58 [OMALIZUMAB] (8180)
60 exp animal experimentation/ or exp animal model/ or exp animal experiment/ or nonhuman/ or exp vertebrate/ (47800438)
61 exp human/ or exp human experimentation/ or exp human experiment/ (37447818)
62 60 not 61 (10354340)
63 59 not 62 [ANIMAL-ONLY REMOVED] (8108)
64 randomized controlled trial/ or controlled clinical trial/ (1258608)
65 exp "clinical trial (topic)"/ (260380)
66 (random#ed or random#ation or randomly or RCT\$1 or placebo*).tw,kw. (2061300)
67 ((singl* or doubl* or trebl* or tripl*) adj (mask* or blind* or dumm*)).tw,kw. (382715)
68 trial.ti. (444068)
69 or/64-68 (2813175)
70 63 and 69 [RCTs] (1574)
71 exp controlled clinical trial/ (1258860)
72 exp "controlled clinical trial (topic)"/ (146668)
73 (control* adj2 trial*).tw,kw. (524307)
74 (nonrandom* or non-random* or quasi-random* or quasi-experiment*).tw,kw. (107171)
75 (nRCT or nRCTs or non-RCT\$1).tw,kw. (1532)
76 (control* adj3 ("before and after" or "before after")).tw,kw. (8682)
77 time series analysis/ (20616)
78 time series.tw,kw. (53142)
79 pretest posttest control group design/ (332)
80 (pre- adj3 post-).tw,kw. (182008)
81 (pretest adj3 posttest).tw,kw. (9447)
82 controlled study/ (5849074)
83 (control* adj2 stud\$3).tw,kw. (485077)
84 control group/ (126446)
85 (control* adj2 group\$1).tw,kw. (1066317)
86 trial.ti. (444068)
87 or/71-86 (8099724)
88 63 and 87 [non-RCTs] (1737)
89 cohort analysis/ (576282)
90 cohort?.tw,kw. (1209614)
91 retrospective study/ (1331424)
92 longitudinal study/ (232036)
93 prospective study/ (929593)
94 (longitudinal or prospective or retrospective).tw,kw. (2648556)
95 follow up/ (1267643)
96 ((followup or follow-up) adj (study or studies)).tw,kw. (114409)
97 observational study/ (180206)

98 (observation\$2 adj (study or studies)).tw,kw. (206957)
99 population research/ (90046)
100 ((population or population-based) adj (study or studies or analys#s)).tw,kw. (44706)
101 ((multidimensional or multi-dimensional) adj (study or studies)).tw,kw. (242)
102 exp comparative study/ (3198822)
103 ((comparative or comparison) adj (study or studies)).tw,kw. (235517)
104 exp case control study/ (1115081)
105 ((case-control* or case-based or case-comparison) adj (study or studies)).tw,kw. (212950)
106 or/89-105 (8523571)
107 63 and 106 [OBSERVATIONAL STUDIES] (1523)
108 70 or 88 or 107 [ALL STUDY DESIGNS] (3017)
109 editorial.pt. (1024292)
110 letter.pt. not (letter.pt. and randomized controlled trial/) (2026060)
111 108 not (109 or 110) [OPINION PIECES REMOVED] (2905)
112 111 use emcxd [EMBASE RECORDS] (2329)
113 conference abstract.pt. (2784228)
114 112 and 113 (757) [EMBASE ABSTRACTS]
115 112 not 113 (1572) [EMBASE – NO ABSTRACTS]
116 54 or 115 [BOTH DATABASES - NO ABSTRACTS] (2275)
117 remove duplicates from 116 (1659) [TOTAL UNIQUE RECORDS – NO ABSTRACTS]
118 117 use emcxd [EMBASE UNIQUE RECORDS - NO ABSTRACTS] (1024)
119 117 not 118 [MEDLINE UNIQUE RECORDS] (635)
120 remove duplicates from 114 (753) [EMBASE UNIQUE RECORDS – ABSTRACTS]
121 117 or 120 (2412) [TOTAL UNIQUE RECORDS – NO ABSTRACTS]
122 120 OR 121 [ALL UNIQUE RECORDS] (2412)

Cochrane Library

Search Name: Omalizumab

Date Run: 23/11/17 12:33:43.233

Description: 2017 Nov 23 - Final - Ottawa Heart Institute

ID Search Hits

#1 [mh Omalizumab] 128

#2 (omalizumab* or xolair*):ti,ab,kw 574

#3 ("HSDB 5742" or HSDB5742 or "HSDB 8176" or HSDB8176 or "hu 901" or hu901 or rhuMabE25 or "rhuMab-E25" or "rhu Mab-E25" or "rhu MADE25" or "UNII-2P471X1Z11"):ti,ab,kw 29

#4 {or #1-#3} 587

#5 Conference abstract:pt 92420

#6 #4 and #5 110

#7 #4 not #5 477

#8 #6 or #7 587

DSR – 2 [reviews]

DARE – 6 [reviews]

CENTRAL – 554 [RCTs]

HTA – 12 [reviews]

NHS EED – 13 [did not download]

REVIEWS

Database: Embase Classic+Embase <1947 to 2017 November 22>, Ovid MEDLINE(R) ALL <1946 to November 22, 2017>
Search Strategy:

- 1 Antibodies, Monoclonal/ (369872)
- 2 Antibodies, Monoclonal, Humanized/ (219381)
- 3 Omalizumab/ (7272)
- 4 (omalizumab\$2 or xolair\$2).tw,kf. (5625)
- 5 (HSDB 5742 or HSDB5742 or HSDB 8176 or HSDB8176 or hu 901 or hu901 or rhuMabE25 or rhuMab-E25 or rhu Mab-E25 or rhu MADE25 or UNII-2P471X1Z11).tw,kf. (115)
- 6 omalizumab.m. (6129)
- 7 or/1-6 [OMALIZUMAB, MONOCLONAL ANTIBODIES] (398267)
- 8 exp Animals/ not (exp Animals/ and Humans/) (15763466)
- 9 7 not 8 [ANIMAL-ONLY REMOVED] (277429)
- 10 limit 9 to systematic reviews [Limit not valid in Embase; records were retained] (120713)
- 11 meta analysis.pt. (94859)
- 12 exp meta-analysis as topic/ (55459)
- 13 (meta-analy* or metanaly* or metaanaly* or met analy* or integrative research or integrative review* or integrative overview* or research integration or research overview* or collaborative review*).tw,kf. (301093)
- 14 (systematic review* or systematic overview* or evidence-based review* or evidence-based overview* or (evidence adj3 (review* or overview*)) or meta-review* or meta-overview* or meta-synthes* or rapid review* or "review of reviews" or technology assessment* or HTA or HTAs).tw,kf. (352968)
- 15 exp Technology assessment, biomedical/ (23338)
- 16 (cochrane or health technology assessment or evidence report).jw. (35315)
- 17 (network adj (MA or MAs)).tw,kf. (15)
- 18 (NMA or NMAs).tw,kf. (3871)
- 19 indirect* compar*.tw,kf. (4237)
- 20 (indirect treatment* adj1 compar*).tw,kf. (541)
- 21 (mixed treatment* adj1 compar*).tw,kf. (1247)
- 22 (multiple treatment* adj1 compar*).tw,kf. (293)
- 23 (multi-treatment* adj1 compar*).tw,kf. (3)
- 24 simultaneous* compar*.tw,kf. (2140)
- 25 mixed comparison?.tw,kf. (41)
- 26 or/11-25 (633723)
- 27 9 and 26 (2544)
- 28 10 or 27 [SYSTEMATIC REVIEWS] (121171)
- 29 (comment or editorial or news or newspaper article).pt. (1813729)
- 30 (letter not (letter and randomized controlled trial)).pt. (2030841)
- 31 28 not (29 or 30) [OPINION PIECES REMOVED] (117806)
- 32 limit 31 to last 2 years (7762)
- 33 32 use emcxd (6957)
- 34 32 not 33 (805) [MEDLINE RECORDS]
- 35 monoclonal antibody/ (191795)
- 36 Omalizumab/ (7272)
- 37 (omalizumab\$2 or xolair\$2).tw,kw. (5722)
- 38 (HSDB 5742 or HSDB5742 or HSDB 8176 or HSDB8176 or hu 901 or hu901 or rhuMabE25 or rhuMab-E25 or rhu Mab-E25 or rhu MADE25 or UNII-2P471X1Z11).tw,kw. (121)
- 39 omalizumab.m. (6129)
- 40 or/35-39 [OMALIZUMAB, MONOCLONAL ANTIBODIES] (199037)
- 41 exp animal experimentation/ or exp animal model/ or exp animal experiment/ or nonhuman/ or exp vertebrate/ (47800438)
- 42 exp human/ or exp human experimentation/ or exp human experiment/ (37447818)
- 43 41 not 42 (10354340)
- 44 40 not 43 [ANIMAL-ONLY REMOVED] (144345)
- 45 meta-analysis/ (232882)
- 46 "systematic review"/ (156727)

47 "meta analysis (topic)"/ (37844)
48 (meta-analy* or metanaly* or metaanaly* or met analy* or integrative research or integrative review* or integrative overview* or research integration or research overview* or collaborative review*).tw,kw. (303723)
49 (systematic review* or systematic overview* or evidence-based review* or evidence-based overview* or (evidence adj3 (review* or overview*)) or meta-review* or meta-overview* or meta-synthes* or "review of reviews" or technology assessment* or HTA or HTAs).tw,kw. (355228)
50 biomedical technology assessment/ (22199)
51 (cochrane or health technology assessment or evidence report).jw. (35315)
52 (network adj (MA or MAs)).tw,kw. (15)
53 (NMA or NMAs).tw,kw. (3890)
54 indirect* compar*.tw,kw. (4292)
55 (indirect treatment* adj1 comparison?).tw,kw. (542)
56 (mixed treatment* adj1 comparison?).tw,kw. (1246)
57 (multiple treatment* adj1 comparison?).tw,kw. (219)
58 (multi-treatment* adj1 comparison?).tw,kw. (3)
59 simultaneous* compar*.tw,kw. (2140)
60 mixed comparison?.tw,kw. (42)
61 or/45-60 (684590)
62 44 and 61 [REVIEWS] (1892)
63 editorial.pt. (1024292)
64 letter.pt. not (letter.pt. not randomized controlled trial/) (9979)
65 62 not (63 or 64) [OPINION PIECES REMOVED] (1872)
66 limit 65 to last 2 years (560)
67 66 use emcxd [EMBASE RECORDS] (516)
68 34 or 67 [BOTH DATABASES] (1321)
69 conference abstract.pt. (2784228)
70 68 not 69 (1253) [ABSTRACTS REMOVED]
71 remove duplicates from 70 (930) [TOTAL UNIQUE RECORDS – NO ABSTRACTS]
72 71 use emcxd [EMBASE UNIQUE RECORDS] (284) [EMBASE UNIQUE RECORDS – NO ABSTRACTS]
73 71 not 72 [MEDLINE UNIQUE RECORDS] (646) [MEDLINE UNIQUE RECORDS – NO ABSTRACTS]
74 68 and 69 (68) [ABSTRACT SET]
75 remove duplicates from 74 (66) [TOTAL UNIQUE REVIEWS WITH ABSTRACTS]
76 75 use emcxd [EMBASE UNIQUE REVIEWS - CONFERENCE ABSTRACTS] (66)
77 75 not 76 [MEDLINE UNIQUE REVIEWS - CONFERENCE ABSTRACTS] (0)
78 71 or 75 [TOTAL UNIQUE REVIEWS - BOTH WITH AND WITHOUT ABSTRACTS] (996)

Supplement 3: Updated Literature Search Strategies

Omalizumab – Primary Studies

Update

2019 Jan 28

MEDLINE

Database: Ovid MEDLINE(R) and Epub Ahead of Print, In-Process & Other Non-Indexed Citations and Daily <1946 to January 25, 2019>

Search Strategy:

-
- 1 Omalizumab/ (1326)
 - 2 (omalizumab\$2 or xolair\$2).tw,kf. (1968)
 - 3 (HSDB 5742 or HSDB5742 or HSDB 8176 or HSDB8176 or hu 901 or hu901 or rhuMabE25 or rhuMab-E25 or rhu Mab-E25 or rhu MADE25 or UNII-2P471X1Z11).tw,kf. (47)
 - 4 omalizumab.m. (1326)
 - 5 or/1-4 [OMALIZUMAB] (2189)
 - 6 exp Animals/ not (exp Animals/ and Humans/) (4539906)
 - 7 5 not 6 [ANIMAL-ONLY REMOVED] (2179)
 - 8 (controlled clinical trial or randomized controlled trial or pragmatic clinical trial).pt. (563462)
 - 9 clinical trials as topic.sh. (185823)
 - 10 (randomi#ed or randomi#ation or randomly or RCT\$1 or placebo*).tw,kf. (899063)
 - 11 ((singl* or doubl* or trebl* or tripl*) adj (mask* or blind* or dumm*)).tw,kf. (162311)
 - 12 trial.ti. (194822)
 - 13 or/8-12 (1262905)
 - 14 7 and 13 [RCTs] (485)
 - 15 controlled clinical trial.pt. (92873)
 - 16 Controlled Clinical Trial/ or Controlled Clinical Trials as Topic/ (98216)
 - 17 (control* adj2 trial*).tw,kf. (240790)
 - 18 Non-Randomized Controlled Trials as Topic/ (445)
 - 19 (nonrandom* or non-random* or quasi-random* or quasi-experiment*).tw,kf. (50412)
 - 20 (nRCT or nRCTs or non-RCT?).tw,kf. (735)
 - 21 Controlled Before-After Studies/ (374)
 - 22 (control* adj3 ("before and after" or "before after")).tw,kf. (3950)
 - 23 Interrupted Time Series Analysis/ (527)
 - 24 time series.tw,kf. (26932)
 - 25 (pre- adj3 post-).tw,kf. (72082)
 - 26 (pretest adj3 posttest).tw,kf. (4849)
 - 27 Historically Controlled Study/ (147)
 - 28 (control* adj2 stud\$3).tw,kf. (214447)
 - 29 Control Groups/ (1604)
 - 30 (control* adj2 group\$1).tw,kf. (458538)
 - 31 trial.ti. (194822)
 - 32 or/15-31 (1134844)
 - 33 7 and 32 [NON-RCTs] (275)
 - 34 exp Cohort Studies/ (1817674)
 - 35 cohort?.tw,kf. (501697)
 - 36 Retrospective Studies/ (727661)
 - 37 (longitudinal or prospective or retrospective).tw,kf. (1131372)

38 ((followup or follow-up) adj (study or studies)).tw,kf. (48479)
39 Observational study.pt. (57079)
40 (observation\$2 adj (study or studies)).tw,kf. (91532)
41 ((population or population-based) adj (study or studies or analys#s)).tw,kf. (16033)
42 ((multidimensional or multi-dimensional) adj (study or studies)).tw,kf. (104)
43 Comparative Study.pt. (1819785)
44 ((comparative or comparison) adj (study or studies)).tw,kf. (107412)
45 exp Case-Control Studies/ (966742)
46 ((case-control* or case-based or case-comparison) adj (study or studies)).tw,kf. (97414)
47 or/34-46 (4183559)
48 7 and 47 [OBSERVATIONAL STUDIES] (386)
49 14 or 33 or 48 [ALL STUDY DESIGNS] (825)
50 (comment or editorial or news or newspaper article).pt. (1290953)
51 (letter not (letter and randomized controlled trial)).pt. (1013949)
52 49 not (50 or 51) [OPINION PIECES REMOVED] (787)
53 (2017 11* or 2017 12* or 2018* or 2019*).dt. (1469274)
54 52 and 53 [UPDATE PERIOD] (102)
55 remove duplicates from 54 (98)

Embase

Database: Embase Classic+Embase <1947 to 2019 January 25>

Search Strategy:

-
- 1 Omalizumab/ (6881)
 - 2 (omalizumab\$2 or xolair\$2).tw,kw. (4611)
 - 3 (HSDB 5742 or HSDB5742 or HSDB 8176 or HSDB8176 or hu 901 or hu901 or rhuMabE25 or rhuMab-E25 or rhu Mab-E25 or rhu MADE25 or UNII-2P471X1Z11).tw,kw. (73)
 - 4 omalizumab.m. (5744)
 - 5 or/1-4 [OMALIZUMAB] (7097)
 - 6 exp animal experimentation/ or exp animal model/ or exp animal experiment/ or nonhuman/ or exp vertebrate/ (26967618)
 - 7 exp human/ or exp human experimentation/ or exp human experiment/ (20624941)
 - 8 6 not 7 (6343748)
 - 9 5 not 8 [ANIMAL-ONLY REMOVED] (7007)
 - 10 randomized controlled trial/ or controlled clinical trial/ (719399)
 - 11 exp "clinical trial (topic)"/ (287389)
 - 12 (randomi#ed or randomi#ation or randomly or RCT\$1 or placebo*).tw,kw. (1253109)
 - 13 ((singl* or doubl* or trebl* or tripl*) adj (mask* or blind* or dumm*)).tw,kw. (226344)
 - 14 trial.ti. (269942)
 - 15 or/10-14 (1785622)
 - 16 9 and 15 [RCTs] (1389)
 - 17 exp controlled clinical trial/ (719690)
 - 18 exp "controlled clinical trial (topic)"/ (163496)
 - 19 (control* adj2 trial*).tw,kw. (321010)
 - 20 (nonrandom* or non-random* or quasi-random* or quasi-experiment*).tw,kw. (62931)
 - 21 (nRCT or nRCTs or non-RCT\$1).tw,kw. (1037)
 - 22 (control* adj3 ("before and after" or "before after")).tw,kw. (5217)
 - 23 time series analysis/ (22337)
 - 24 time series.tw,kw. (30526)
 - 25 pretest posttest control group design/ (365)
 - 26 (pre- adj3 post-).tw,kw. (128415)
 - 27 (pretest adj3 posttest).tw,kw. (5526)
 - 28 controlled study/ (6434933)
 - 29 (control* adj2 stud\$3).tw,kw. (287418)
 - 30 control group/ (122318)
 - 31 (control* adj2 group\$1).tw,kw. (662618)
 - 32 trial.ti. (269942)
 - 33 or/17-32 (7312525)
 - 34 9 and 33 [non-RCTs] (1718)
 - 35 cohort analysis/ (436521)
 - 36 cohort?.tw,kw. (832760)
 - 37 retrospective study/ (738486)
 - 38 longitudinal study/ (122153)
 - 39 prospective study/ (500774)
 - 40 (longitudinal or prospective or retrospective).tw,kw. (1706430)
 - 41 follow up/ (1397659)
 - 42 ((follow up or follow-up) adj (study or studies)).tw,kw. (69158)
 - 43 observational study/ (159477)
 - 44 (observation\$2 adj (study or studies)).tw,kw. (141492)

45 population research/ (97616)
46 ((population or population-based) adj (study or studies or analys#s)).tw,kw. (23128)
47 ((multidimensional or multi-dimensional) adj (study or studies)).tw,kw. (143)
48 exp comparative study/ (1336074)
49 ((comparative or comparison) adj (study or studies)).tw,kw. (138498)
50 exp case control study/ (153948)
51 ((case-control* or case-based or case-comparison) adj (study or studies)).tw,kw. (124699)
52 or/35-51 (4960214)
53 9 and 52 [OBSERVATIONAL STUDIES] (1539)
54 16 or 34 or 53 [ALL STUDY DESIGNS] (2902)
55 editorial.pt. (595541)
56 letter.pt. not (letter.pt. and randomized controlled trial/) (1051614)
57 54 not (55 or 56) [OPINION PIECES REMOVED] (2786)
58 conference abstract.pt. (3269452)
59 57 not 58 [CONFERENCE ABSTRACTS REMOVED] (1818)
60 (201711* or 201712* or 2018* or 2019*).dc. (2237025)
61 59 and 60 [UPDATE PERIOD - CONFERENCE ABSTRACTS REMOVED] (320)
62 57 and 58 [CONFERENCE ABSTRACTS] (968)
63 60 and 62 [UPDATE PERIOD - CONFERENCE ABSTRACTS] (236)

Cochrane Library

Search Name: Omalizumab
Date Run: 28/01/2019 17:03:41
Comment: 2017 Nov 23 - Final - Ottawa Heart Institute

ID	Search	Hits
#1	[mh Omalizumab]	206
#2	(omalizumab* or xolair*):ti,ab,kw	675
#3	("HSDB 5742" or HSDB5742 or "HSDB 8176" or HSDB8176 or "hu 901" or hu901 or rhuMabE25 or "rhuMab-E25" or "rhu Mab-E25" or "rhu MADE25" or "UNII-2P471X1Z11"):ti,ab,kw	30
#4	{or #1-#3}	689
#5	Conference abstract:pt	123620
#6	#4 and #5 with Cochrane Library publication date Between Nov 2017 and Jan 2019, in Trials	45
#7	#4 not #5 with Cochrane Library publication date Between Nov 2017 and Jan 2019, in Trials	100
#8	#6 or #7	145

Supplement 4: Study Eligibility Criteria

INCLUSION	EXCLUSION
Population	
Males and females aged ≥ 12 years who: - have moderate to severe persistent allergic asthma confirmed by a positive skin prick test or in vitro reactivity to a perennial aeroallergen and inadequate control with inhaled corticosteroids OR - have chronic idiopathic urticaria that is symptomatic despite H1 antihistamine treatment.	- Patients under 12 years of age - Patients with non-atopic asthma
Intervention	
Subcutaneous omalizumab every two or four weeks with no restrictions on dose	Omalizumab administered using another route of administration or dose schedule
Comparators	
- Placebo - Standard of care - Sodium cromoglycate - No comparator	All other comparators
Outcomes*	
<u>Primary</u> - Study-emergent solid epithelial cancer (e.g. squamous cell carcinoma, adenocarcinoma, transitional cell carcinoma, or basal cell carcinoma) <u>Secondary</u> - Study-emergent solid epithelial cancer by organ system - Study-emergent solid epithelial cancer by histological type. If the histological type of cancer was not clear but was potentially an epithelial cancer, it was eligible. - Progression† of solid epithelial cancer during the study treatment period. (cont'd)	All non-epithelial cancers (e.g. neuroendocrine tumours, sarcomas, leukemias, lymphomas, myelomas, and brain and spinal cord cancers)

INCLUSION	EXCLUSION
Study design	
Interventional studies: • Randomized controlled trials • Quasi-randomized trials • Controlled clinical trials Observational studies: • Cohort studies • Case-control studies	• Systematic reviews[‡] • Narrative reviews • Case series (if fewer than 10 patients) • Case reports • Abstracts • Research letters
Treatment duration	
• 52 weeks of continuous omalizumab treatment[€]	• Non-continuous treatment with omalizumab, or treatment for less than 52 weeks
Language	
• All languages were eligible	• No restrictions

^{*}Cancers were only eligible for inclusion if they developed during the study period

[†]Progression was determined based on evidence of recurrence, worsening, or progression of stage.

[‡]Systematic reviews published from 2015 and later were retained and their reference lists were screened for potentially eligible studies.

[€]All study participants were required to have had continuous and long-term treatment with omalizumab. A minimum treatment duration of 52 weeks was established during the protocol development stage; however, a post-hoc decision was made to include interventional studies in which the final dose of omalizumab was administered at 48 weeks because omalizumab is administered every two or four weeks. Furthermore, observational studies had less strict controls on treatment duration, thus, these types of studies were eligible if their participants were treated for a minimum of 40 weeks.

Supplement 5: Quality Assessment Methodology

Randomized Controlled Trials

Randomized controlled trials (RCTs) were assessed for risk of bias (ROB) using Cochrane's ROB tool. We considered allocation concealment, blinding of outcome assessors, and incomplete outcome data (i.e., attrition) to be the domains of key importance in evaluating each RCT's overall ROB. Final judgments were made using the suggested approach as described in the Cochrane Handbook for Systematic Reviews of Interventions [36]. Specifically, an RCT was considered to be low in overall ROB if it was assessed low ROB ratings for all key domains, unclear in overall ROB if it received at least one unclear ROB rating in a key domain, and high in overall ROB if one or more key domains were judged to be high in ROB.

Comparative Observational Studies

The only included comparative observational study reporting at least one outcome of interest was assessed for overall quality using the Newcastle Ottawa Scale (NOS). For this review, the number of exacerbations per year prior to entering the study was considered the most important variable that studies should have adjusted for. Variables of secondary importance were: FEV1 % predicted, age, sex, and length of omalizumab use before study entry. We set a minimum required treatment duration (described previously) to ensure that each study follow-up period was reasonably long enough for an outcome to have occurred. Finally, we determined that a completion rate of greater than 80% was necessary to conclude that loss to follow-up was unlikely to have introduced bias.

Non-comparative Observational Studies

The Joanna Briggs Institute (JBI) checklist for prevalence studies was used to appraise the quality of non-comparative observational studies. There is no explicit guidance on determining the overall quality of a study using the results of a NOS assessment. As such, we have chose to follow the thresholds for converting the NOS scale to the Agency for Healthcare Research and Quality (AHRQ) standards (see S5 Table 1, below), which allowed us to objectively classify studies as being of good, fair, or poor overall quality.

Table S5 a: Thresholds for Converting NOS Scores to AHRQ Overall Study Quality Standards

NOS Assessment Criteria	AHRQ Study Quality Standard
3 or 4 stars awarded in selection domain AND 1 or 2 stars awarded in comparability domain AND 2 or 3 stars awarded in outcome/exposure domain	Good quality study
2 stars awarded in selection domain AND 1 or 2 stars awarded in comparability domain AND 2 or 3 stars awarded in outcome/exposure domain	Fair quality study
0 or 1 star awarded in selection domain OR 0 stars awarded in comparability domain OR 0 or 1 stars awarded in outcome/exposure domain	Poor quality study

NOS = Newcastle-Ottawa Scale, AHRQ = Agency for Healthcare Research and Quality

Supplement 6: List of Included Studies

STUDIES IDENTIFIED FROM BIBLIOGRAPHIC DATABASES

Buhl et al. (Parent study in **bold**)

1. **Buhl R, Soler M, Matz J, et al. Omalizumab provides long-term control in patients with moderate-to-severe allergic asthma. *Eur Respir J.* 2002;20:73-78.**
2. Buhl R, Hanf G, Soler M, et al. The anti-IgE antibody omalizumab improves asthma-related quality of life in patients with allergic asthma. *Eur Respir J.* 2002;20:1088-1094.

The EXCELS Study (Parent study in **bold**)

3. **Long A, Rahmaoui A, Rothman KJ, et al. Incidence of malignancy in patients with moderate-to-severe asthma treated with or without omalizumab. *J Allergy Clin Immunol.* 2014;134:560-567.**
4. Long AA, Fish JE, Rahmaoui A, et al. Baseline characteristics of patients enrolled in EXCELS: a cohort study. *Ann Allergy Asthma Immunol.* 2009;103:212-219.
5. Eisner MD, Zazzali JL, Miller MK, Bradley MS, Schatz M. Longitudinal changes in asthma control with omalizumab: 2-year interim data from the EXCELS Study. *J Asthma.* 2012;49:642-648.
6. Iribarren C, Rahmaoui A, Long AA, et al. Cardiovascular and cerebrovascular events among patients receiving omalizumab: Results from EXCELS, a prospective cohort study in moderate to severe asthma. *J Allergy Clin Immunol.* 2017;139:1489-1495.
7. Chen H, Eisner MD, Haselkorn T, Trzaskoma B. Concomitant asthma medications in moderate-to-severe allergic asthma treated with omalizumab. *Respir Med.* 2013;107:60-67.
8. Janson SL, Solari PG, Trzaskoma B, Chen H, Haselkorn T, Zazzali JL. Omalizumab adherence in an observational study of patients with moderate to severe allergic asthma. *Ann Allergy Asthma Immunol.* 2015;114:516-521.

The EXPERIENCE Study (Parent study in **bold**)

9. **Braunstaal GJ, Chen CW, Maykut R, Georgiou P, Peachey G, Bruce J. The eXpeRience registry: the 'real-world' effectiveness of omalizumab in allergic asthma. *Respir Med.* 2013;107:1141-1151.**
10. Barbosa MP, Almeida ABd, Pereira C, et al. Real-life efficacy and safety of omalizumab in Portuguese patients with persistent uncontrolled asthma. *Rev Port Pneumol (Barc).* 2015;21:151-156.
11. Braunstaal GJ, Chlumsky J, Peachey G, Chen CW. Reduction in oral corticosteroid use in patients receiving omalizumab for allergic asthma in the real-world setting. *Allergy Asthma Clin Immunol.* 2013;9:47, 2013.

The EXTRA study (parent study in **bold**)

12. **Hanania NA, Alpan O, Hamilos DL, et al. Omalizumab in severe allergic asthma inadequately controlled with standard therapy: a randomized trial. *Ann Intern Med.* 2011;154:573-582.**
13. Hanania NA, Wenzel S, Rosen K, et al. Exploring the effects of omalizumab in allergic asthma: an analysis of biomarkers in the EXTRA study. *Am J Respir Crit Care Med.* 2013;187(8):804-811.
14. Zhu R, Zheng Y, Putnam WS, et al. Population-based efficacy modeling of omalizumab in patients with severe allergic asthma inadequately controlled with standard therapy. *AAPS Journal.* 2013;15:559-570.
(Companion clinical trial record listed with other records retrieved from clinical trial registries)

PROSPERO (parent study in **bold**)

15. **Chippes BE, Zeiger RS, Luskin AT, et al. Baseline asthma burden, comorbidities, and biomarkers in omalizumab-treated patients in PROSPERO. *Ann Allergy Asthma Immunol.* 2017; 2017 Oct 17.**
16. Casale TB, Luskin AT, Busse W, et al. Omalizumab Effectiveness by Biomarker Status in Patients with Asthma: Evidence From PROSPERO, A Prospective Real-World Study. *J Allergy Clin Immunol Pract* 2019;7(1):156-64.

XPORT (parent study in **bold**)

17. **Ledford D, Busse W, Trzaskoma B, et al. A randomized multicenter study evaluating Xolair persistence of response after long-term therapy. *J Allergy Clin Immunol.* 2017;140:162-169. (Companion NCT listed with other records retrieved from clinical trial registries)**

Included Unique Studies

18. Adachi M, Kozawa M, Yoshisue H, et al. Real-world safety and efficacy of omalizumab in patients with severe allergic asthma: A long-term post-marketing study in Japan. *RespirMed* 2018;141:56-63.
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INCLUDED STUDIES IDENTIFIED FROM CLINICAL TRIAL REGISTRIES

Companion Clinical Trial Registry Studies			
Companion NCT to XPORT			
NCT01125748	Genentech, Inc.	A Study Evaluating the Persistency of Response With or Without Xolair (Omalizumab) After Long-term Therapy	https://ClinicalTrials.gov/show/NCT01125748
Companion NCTs to EXTRA			
NCT00314574	University of Mississippi Medical Center; Novartis (collaborator)	Soluble CD23 expression in asthma patients treated with OMA	https://clinicaltrials.gov/ct2/show/NCT00226200
NCT00314574	Genentech, Inc.	A Phase IIIb Multicenter, Randomized, Double-Blind, Placebo-Controlled Study of Xolair in Subjects With Moderate to Severe Persistent Asthma Who Are Inadequately Controlled With High-Dose Inhaled Corticosteroids and Long-Acting Beta-Agonists.	https://ichgcp.net/clinical-trials-registry/NCT00314574
'Other' Companion NCT records			
NCT03580369	Novartis	A Phase III Study of Efficacy and Safety of Ligelizumab in the Treatment of CSU in Adolescents and Adults Inadequately Controlled With H1-antihistamines.	https://clinicaltrials.gov/show/nct03580369
NCT03580356	Novartis	A Phase III Study of Efficacy and Safety of Ligelizumab in the Treatment of CSU in Adolescents and Adults Inadequately Controlled With H1-antihistamines.	https://clinicaltrials.gov/show/nct03580356
Unique Records Retrieved from Clinical Trials.gov			
NCT00242359	Bernstein Clinical Research Center	A pilot study investigating the effect of omalizumab (Xolair) in work-related animal induced asthma	https://clinicaltrials.gov/ct2/show/NCT00242359
NCT00208234	Creighton University; Genentech, Inc. (collaborator)	Effect of Xolair on airway hyperresponsiveness	https://clinicaltrials.gov/ct2/show/results/NCT00208234
NCT03476109	Multiple- see registry for further detail	Study of Magnitude and Prediction of Response to Omalizumab and Mepolizumab in Adult Severe Asthma	https://clinicaltrials.gov/show/nct03476109
NCT01922037	Hoffmann-La Roche	A Study in Participants With Asthma Initiating Treatment With Omalizumab (Xolair)	https://ClinicalTrials.gov/show/NCT01922037
NCT02921178	Ajou University School of Medicine	Effects of Omalizumab Compared to Non-Omalizumab Treatment in Asthma Patients	https://ClinicalTrials.gov/show/NCT02921178
NCT00670930	Novartis Pharmaceutica Is Genentech, Inc. Novartis	Efficacy of Omalizumab in Adults (18-60 Years of Age) With Moderate-Severe, Persistent Allergic Asthma, Despite Receiving Inhaled Corticosteroids and Long Acting Beta-agonists	https://ClinicalTrials.gov/show/NCT00670930

NCT00639691	Novartis	A Compassionate Access Protocol to Assess the Safety of Xolair™ (Omalizumab) in Patients (≥ 6 Years Old) With Severe Allergic Asthma Who Remain Symptomatic Despite Optimal Therapy	https://ClinicalTrials.gov/show/NCT00639691
NCT00377572	National Institute of Allergy and Infectious Diseases (NIAID) Inner-City Asthma Consortium	Inner-City Anti-IgE Therapy for Asthma	https://ClinicalTrials.gov/show/NCT00377572
NCT00482508	Novartis Genentech, Inc.	Safety and Tolerability of Omalizumab in Poorly Controlled Moderate to Severe Asthma Patients	https://ClinicalTrials.gov/show/NCT00482508
NCT02742805	Selina Gierer, D.O. University of Kansas Medical Center	Sustained Effect of Urticaria Remission With Relatively High Dose Vitamin D Supplementation After Omalizumab Discontinuation	https://ClinicalTrials.gov/show/NCT02742805
NCT00482248	Novartis Genentech, Inc.	Safety and Tolerability of Omalizumab in Adults and Adolescents With Severe Allergic Asthma	https://ClinicalTrials.gov/show/NCT00482248
NCT00109187	Genentech, Inc.	An Extension Study of Xolair in Moderate to Severe, Persistent Asthma Patients Who Completed Study Q2143g	https://ClinicalTrials.gov/show/NCT00109187
NCT00109200	Genentech, Inc.	A Continued Access Protocol to Provide Xolair to Patients With Severe Allergic Asthma	https://ClinicalTrials.gov/show/NCT00109200
NCT00813748	Genentech, Inc.	Pharmacosurveillance Data Repository of Patients With and Without History of Anaphylactic Reactions Subsequent to Xolair Dosing	https://ClinicalTrials.gov/show/NCT00813748
NCT01912872	Novartis Pharmaceuticals Novartis	Study to Assess the Efficacy and Safety of Omalizumab Treatment on ICS Reduction for Severe IgE-mediated Asthma	https://ClinicalTrials.gov/show/NCT01912872
NCT01460862	Novartis Pharmaceuticals Novartis	Impact of Omalizumab on Corticosteroid Use, Emergency Room Visits and Hospitalizations	https://ClinicalTrials.gov/show/NCT01460862
NCT00377390	National Institute of Allergy and Infectious Diseases (NIAID)	ICATA Asthma Mechanistic Study	https://ClinicalTrials.gov/show/NCT00377390
NCT01776177	Joseph D. Diaz, MD Genentech, Inc. Allergy & Asthma Research Center, San Antonio, TX	The REALITY Study - a Real-life Long-term Analysis of Xolair Therapy	https://ClinicalTrials.gov/show/NCT01776177

NCT00367016	University of California, Davis	Immunologic Basis of Anti-IgE Therapy (Study II: On Patients With Asthma)	https://ClinicalTrials.gov/show/NCT00367016
NCT00283504	Children's Hospital of The King's Daughters Novartis Genentech, Inc.	A Description of Inflammatory Cell Types In Moderate to Severe Pediatric Asthma: Eosinophilic and Non Eosinophilic Sputum Markers While on Anti-IgE Therapy	https://ClinicalTrials.gov/show/NCT00283504
NCT01397760	Iara Nely Fiks, M.D.	Retrospective Study for Description of The Use Of Omalizumab In Patients With Difficult To Control Asthma	https://ClinicalTrials.gov/show/NCT01397760
NCT00252135	Genentech, Inc.	A Study of Xolair to Evaluate Effectiveness and Long-Term Safety in Patients With Moderate to Severe Asthma	https://ClinicalTrials.gov/show/NCT00252135
NCT00350376	Ovation Research Group Genentech, Inc.	Impact of Asthma Treatments on Daily Activities	https://ClinicalTrials.gov/show/NCT00350376
Records retrieved from the World Health Organization's International Clinical Trials Registry Portal			
CIGE025AIN01	Novartis Healthcare Private Ltd.	A Post Marketing Surveillance study (EASE) to study the efficacy & safety of Xolair (Omalizumab) in IgE mediated Asthma	http://www.ctri.nic.in/Clinicaltrials/pmaindet2.php?trialid=1283
CIGE025B1301	Novartis Pharma	An extension study to CIGE025B1301 to evaluate the long-term safety, tolerability and efficacy of omalizumab in Japanese children	http://www.clinicaltrials.jp/user/showCteDetailE.jsp?japicid=JapicCTI-111453
CIG025A2426	University Hospital Gent	Clinical and biological effects of Anti-IgE (Omalizumab) in patients with bilateral nasal polyposis and asthma	https://www.clinicaltrialsregister.eu/ctr-search/search?query=eudract_number:2006-003524-11
UMIN000002765	Atami Hospital International University of Health and Welfare	Clinical effects of treatment with omalizumab in patients with asthma	https://upload.umin.ac.jp/cgi-open-bin/ctr_e/ctr_view.cgi?recptno=R000003360
UMIN000002389	Kyoto University Graduate School of Medicine	Comprehensive study to examine the effects of omalizumab in patients with bronchial asthma	https://upload.umin.ac.jp/cgi-open-bin/ctr_e/ctr_view.cgi?recptno=R000002935
2009-010914-3	Dr. Christian Domingo	Eficacia clínica y cambios histológicos secundarios al tratamiento con omalizumab en asmáticos alérgicos en estadio V de la gina - CHD-PI08	https://www.clinicaltrialsregister.eu/ctr-search/search?query=eudract_number:2009-010914-31

2010-024113-31	Instituto Científico y Tecnológico de Navarra	Ensayo clínico multicéntrico, doble ciego, controlado con placebo, cruzado (2x2) con aleatorización de la secuencia, para evaluar la eficacia y seguridad de Omalizumab (Xolair®, Novartis) en una nueva indicación: urticaria crónica autoinmune y no autoinmune	https://www.clinicaltrialsregister.eu/ctr-search/search?query=eudract_number:2010-024113-31
2006-002771-40	S.G.O. Johansson, MD PhD	Importance of IgE antibody fraction size on allergen sensitivity of basophils from cat allergic patients on Xolair. A pilot study	https://www.clinicaltrialsregister.eu/ctr-search/search?query=eudract_number:2006-002771-40
2009-012108-15	Mainz University Hospital	Korrelation von freiem IgE mit klinischen Parametern bei Asthma-Patienten unter Therapie mit Omalizumab, einem monoklonalen Antikörper gegen körpereigenes IgE - Freies IgE	https://www.clinicaltrialsregister.eu/ctr-search/search?query=eudract_number:2009-012108-15
CIGE025AMX02	Novartis	Multicentric, Open-label, Randomized, Parallel-group Study to Evaluate the Efficacy and Safety of Omalizumab in a 12-Month Period, in Patients with Severe IgE-mediated Asthma Inadequately Controlled with High Doses of Corticosteroids. MEXIC Study	https://www.clinicaltrialsregister.eu/ctr-search/search?query=eudract_number:2016-004315-13
2009-014582-51	Technische Universität München	Pilot study - sequential combination therapy using selective immunoglobulin apheresis and omalizumab in patients with severe atopic dermatitis and elevated total IgE levels	https://www.clinicaltrialsregister.eu/ctr-search/search?query=eudract_number:2009-014582-51
CIGE025AGB04	Novartis	The impact of omalizumab treatment in UK clinical practice for asthma	http://isrctn.com/ISRCTN55772104
DRKS00006046	Universitätsklinikum Gießen und Marburg	Therapy monitoring of omalizumab in children and adolescents with severe allergic asthma	http://www.drks.de/DRKS00006046
Other clinical trial registries			
Companion trials			
Cige0250011E	Novartis	An open-label extension to assess long-term safety and tolerability of omalizumab treatment in adolescents and adults with severe allergic asthma who participated in the 32-week core study.	http://www.novctrd.com/ctrWebApp/clinicaltrialrepository/displayFile.do?trialResult=1609
Cige0250011E2	Novartis	An open-label extension study to assess long term safety and tolerability of omalizumab treatment in adults and adolescents with severe allergic asthma who participated in the 52 week CIGE025 0011E2 study.	http://www.novctrd.com/ctrwebapp/clinicaltrialrepository/displayfile.do?Trialresult=2314

Supplement 7: Detailed Study Characteristics

Author (Year), Study Name, Registry #	Country	Treatment Duration	RCT: Study Phases	Cross- over or switch groups	Funding	Inclusion criteria	Exclusion criteria
RANDOMIZED CONTROLLED TRIALS							
Ledford (2017), XPORT, NCT01125748	USA (multicenter)	48 weeks	1. Dose reduction of concomitant treatment	Yes	Genentech & Novartis	17-70 years old; continuous OMA exposure ($\leq 25\%$ scheduled doses missed); standard USA prescribed dose; received stable doses of other asthma therapies for ≥ 2 mo before enrollment; most participants were recruited from EXCELS	Participation in another clinical study; acute asthma exacerbation within 2 mo of screening requiring start on or increase in systemic corticosteroids, doubling ICS dose, or emergency department/ hospitalization within 2 mo of study entry; significant or unstable systemic disease; active lung disease other than asthma; 10 pack-year or longer smoking history; use of an experimental drug within 30 days before study screening; pregnancy, lactation, or any planned pregnancy during the study year; or increased serum IgE levels for reasons other than allergy

Author (Year), Study Name, Registry #	Country	Treatment Duration	RCT: Study Phases	Cross- over or switch groups	Funding	Inclusion criteria	Exclusion criteria
Hanania (2011), EXTRA, NCT00314574	USA, Canada	48 weeks	1. Run-in period (pre- randomization); 2. Stable phase with concomitant treatment	No	Genentech & Novartis	12-75 years; history of severe allergic asthma for ≥ 1 year before screening; diagnosis of asthma by physician investigators at each site with NAEPP guideline criteria; asthma was not well-controlled (i.e. persistent asthma symptoms of ≥ 1 night-time awakening/week and daytime asthma symptoms requiring rescue medication for ≥ 2 days/wk during 4 wks before screening and for 2 consecutive wks of up to 4 wks before randomization; despite treatment with high-dose ICS and LABAs with/without other controllers (including OCS); ≥ 1 documented asthma exacerbation in past 12 mo (i.e. increased asthma symptoms requiring treatment with systemic corticosteroid rescue therapy); objective evidence of allergy to a relevant perennial aeroallergen (i.e. positive skin test result or in vitro response (RAST) to dog, cat, cockroach, Dermatophagoides farinae (dust mite), or D. pteronysinus) in 12 mo before screening; baseline prebronchodilator FEV ₁ of 40-80% predicted values; serum IgE level of 30- 700 IU/mL; body weight 30- 150 kg	Asthma exacerbation requiring intubation in 12 mo before screening or exacerbation requiring treatment with systemic corticosteroids (or an increase in baseline dose of OCS) in 30 days before screening; active lung disease other than asthma; treatment with OMA in 12 mo before screening; elevated serum IgE levels unrelated to allergy (e.g. parasite infections, hyper IgE syndrome, Wiskott-Aldrich syndrome or bronchopulmonary aspergillosis); smoking history of ≥ 10 pack-years

Author (Year), Study Name, Registry #	Country	Treatment Duration	RCT: Study Phases	Cross- over or switch groups	Funding	Inclusion criteria	Exclusion criteria
Buhl (2002)	Multi-national	52 weeks (28 weeks + 24 weeks extension phase)	1. Run-in period (pre- randomization); 2. Stable phase with concomitant treatment; 3. Dose reduction of concomitant treatment; 4. Extension phase (post- randomization)	Not Reported	Genentech & Novartis	12–75 years old; diagnosis of asthma for ≥ 1 year based on ATS criteria; positive skin-prick test to ≥ 1 allergen (<i>Dermatophagoides farinae</i> , <i>D. pteronyssinus</i> , dog or cat); serum total IgE level ≥ 30 and ≤ 700 IU/mL; body weight ≤ 150 kg; baseline pre-bronchodilator FEV ₁ baseline $\geq 40\%$ and $\leq 80\%$ predicted and increasing by $\geq 12\%$ within 30 min of taking inhaled salbutamol; mean total daily symptom score of ≥ 3.0 (max 9) during the 14 days prior to randomization; treatment with ICS (500-1200 mg/day BDP equiv for ≥ 3 mo prior to randomization; use of B2- adrenoceptor agonists on as- needed or regular basis; stable asthma with no significant change in regular medication; no acute exacerbation requiring additional corticosteroid treatment for ≥ 1 mo prior to screening visit	Patients regularly taking OCS

Author (Year), Study Name, Registry #	Country	Treatment Duration	RCT: Study Phases	Cross- over or switch groups	Funding	Inclusion criteria	Exclusion criteria
COMPARATIVE OBSERVATIONAL STUDY							
Long (2014), EXCELS, NCT00252135	USA	Median (range): 36.6 (0-73) months	Not Applicable	Yes	Genentech & Novartis	≥12 years old; moderate-to-severe allergic physician-diagnosed asthma; positive skin test result or in vitro reactivity to a perennial aeroallergen (eg, RAST); patients willing to participate for 5-year study duration; study protocol amendment allowed patients with prior malignant condition, premalignant condition, or current investigation for cancer diagnosis	Acute asthma exacerbation within 2 wks before screening; acute flare of significant systemic disease (eg, infection, hematologic, renal, hepatic, cardiovascular, or gastrointestinal diseases); recent disease-related hospitalization within the previous 2 mo; diagnosis of cystic fibrosis; contraindication for OMA therapy
NON-COMPARATIVE OBSERVATIONAL STUDIES							
Chipps (2017), PROSPERO, NCT01922037	USA	12 months	Not Applicable	Not Applicable	Genentech & Novartis	≥12 years old ; allergic asthma; no OMA within previous year	Prior allergic reaction to OMA; received experimental drug within 3 mo of study enrollment
Tat (2016)	Turkey	Mean (SD): 35.6 (17.8) months	Not Applicable	Not Applicable	NR	Uncontrolled severe persistent allergic asthma sensitivity to ≥1 perennial allergen; increased IgE levels; elderly adults >64 years old	<65 years old
Gouder (2015)	Malta	52 weeks	Not Applicable	Not Applicable	No funding	Adults with uncontrolled severe IgE-mediated allergic asthma despite compliance with high dose ICS and LABA and satisfactory inhaler technique; eligible to start OMA; high IgE level; reduced FEV ₁ ; frequent day/night-time symptoms; recurrent exacerbations during the previous year; patients who were expected to complete 52 weeks OMA between 2011 and 2013	Not reported

Author (Year), Study Name, Registry #	Country	Treatment Duration	RCT: Study Phases	Cross- over or switch groups	Funding	Inclusion criteria	Exclusion criteria
Vieira (2014)	Portugal	Not reported	Not Applicable	Not Applicable	NR	Adults with uncontrolled severe allergic asthma despite treatment with high doses of ICS (>1000 micrograms budesonide/day or equiv and LABA) or patients suggested by treating physician to start on OMA with agreement of two or more medical experts; perennial allergen sensitization (by skin prick tests and/or specific IgE assay); reduction in lung function (FEV ₁ <80% of predicted); frequent day/night-time asthma symptoms; multiple exacerbations; need of systemic corticosteroids, emergency services or hospitalizations during previous year	Not reported
Braunstahl (2013), eXpeRience	Multi-national	2 years	Not Applicable	Not Applicable	Genentech & Novartis	Patients meeting local labeling requirements for OMA; started OMA within previous 15 wks; protocol amended for Canada to allow 20 patients who may have started earlier due to enrollment in a real-world prospective study (XCEED study)	Patients currently enrolled and receiving treatment in a clinical trial of OMA or another asthma medication; if they had received OMA in past 18 mo

Author (Year), Study Name, Registry #	Country	Treatment Duration	RCT: Study Phases	Cross- over or switch groups	Funding	Inclusion criteria	Exclusion criteria
Mansur (2017)	UK (single center)	Mean (SD), range: 60.7 (30.9), 23- 121 months	Not Applicable	Not Applicable	No funding	Patients with severe allergic asthma treatment with 150-600 mg OMA q2w or q4w for >23 mo following EU label and NICE guidelines; patients classified as OMA responders following physician's GETE assessment after 16 wks treatment trial (only patients who responded at 16 wks and remained on long-term treatment up to March 2013 were included in analysis)	Patients who did not respond to omalizumab for 16 weeks (those who did not remain on long-term treatment)
Al-Ahmad (2018)	Kuwait (single center)	1 to 10 years	Not applicable	Not applicable	None	Patients had severe allergic asthma and were stepped up to treatment with OMA (level 5 GINA)	Not reported

Author (Year), Study Name, Registry #	Country	Treatment Duration	RCT: Study Phases	Cross- over or switch groups	Funding	Inclusion criteria	Exclusion criteria
Yorgancıoğlu (2018)	Turkey (multicentre)	Minimum 16 weeks to 5 years	Not applicable	Not applicable	Novartis	Patients with severe allergic- asthma, aged ≥ 18 years at the initiation of omalizumab. Patients must have received at least 1 dose of OMA as part of routine clinical practice. Omalizumab treatment had been initiated according to the following criteria: severe, persistent allergic asthma (according to GINA guidelines), poor control of asthmatic disease despite ongoing treatment with high doses of ICS in association with LABAs, total serum IgE 30 to 1500 IU/mL, evidence of sensitization by prick test or specific IgE detection to at least 1 perennial allergen and suitable according to the dose table based on the body weight and IgE level.	Patients in the participating centers were routinely assessed to exclude an alternative diagnosis that could mimic or accompany severe allergic asthma (e.g. bronchopulmonary aspergillosis and vasculitides)

Supplement 8: Quality Assessment Results

Table S8 a: Results of the ROB Assessments of Included RCTs Reporting at Least One Outcome

Cochrane Risk of Bias Domain	Ledford et al., 2017 (XPORT)	Hanania et al., 2011 (EXTRA)	Buhl et al., 2002
Random sequence generation	Low	Low	Unclear
Allocation concealment*	Low	Low	Unclear
Blinding of participants and personnel	Low	Low	Low
Blinding of outcome assessors*	Unclear	Low	Unclear
Incomplete outcome data (Primary outcome: study-emergent solid epithelial cancer) *	Low	Low	High
Incomplete outcome data (Secondary outcome: study-emergent solid epithelial cancer by organ system) *	N/A	Low	High
Incomplete outcome data (Secondary outcome: study-emergent solid epithelial cancer by histological type) *	Low	N/A	N/A
Incomplete outcome data (Secondary outcome: progression of solid epithelial tumour) *	N/A	N/A	N/A
Selective outcome reporting	Low	Unclear	Unclear
Overall within-study ROB	UNCLEAR	LOW	HIGH

* These are the domains of key importance to our overall within-study ROB assessment; see Supplement 4 for further details.

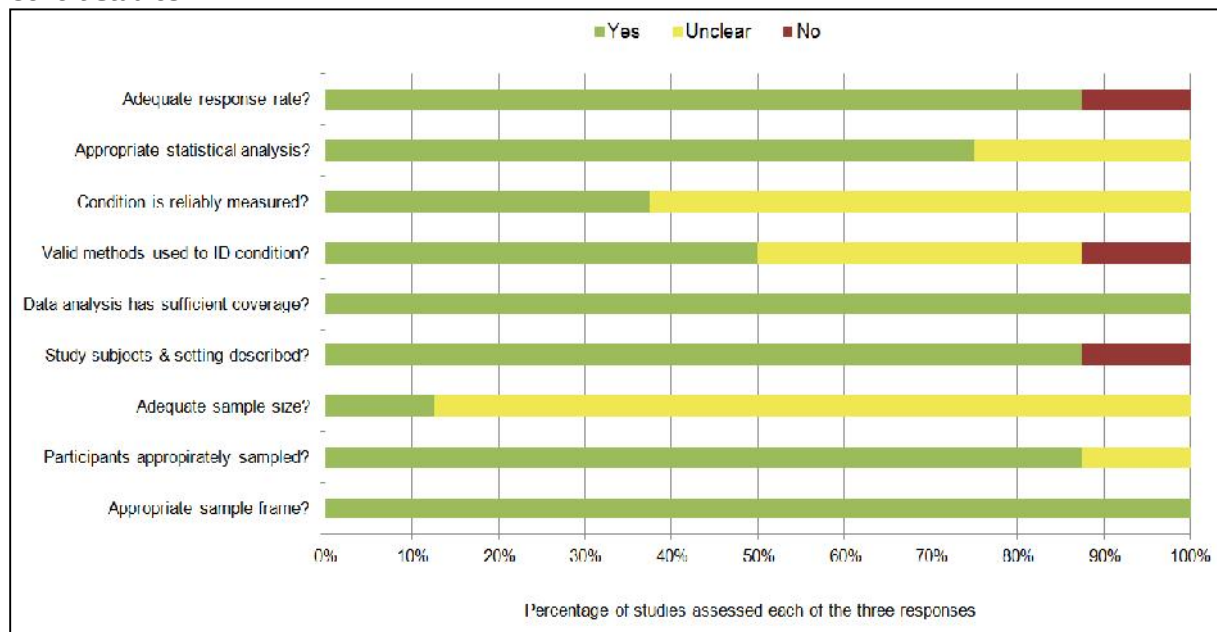
N/A = study did not report on the outcome; therefore, a judgment is 'not applicable'

Table S8 b: Results of the Newcastle-Ottawa Scale Assessment of the Study by Long et al.

Outcome Category	Assessment	Stars Awarded
Selection		
Representativeness of the exposed cohort	Truly representative of the average allergic asthma patient treated with omalizumab in the community	*
Selection of the non-exposed cohort	Drawn from the same community as the exposed cohort	*
Ascertainment of exposure	Written self report	
Demonstration that outcome of interest was not present at start of study	No	
Comparability		
Comparability of cohorts on the basis of the design or analysis	Study did not control for the number of asthma exacerbations per year (most important factor)	
	Study controlled for FEV1 % predicted, age, sex, and length of omalizumab use before study entry (additional important factors)	*
Outcome		
Assessment of outcome	Independent blind assessment	*
Was follow-up long enough for outcomes to occur?	Yes, participants were treated with omalizumab for a minimum of 40 weeks (both cohorts had a median follow-up of approximately 5 years)	*
Adequacy of follow-up of cohorts	Subjects lost to follow-up unlikely to introduce bias (<20%)	*
Overall Assessment*		
Selection domain- 2 stars Comparability domain- 1 star Outcome domain- 3 stars		Fair quality study

* Based on quality based on the thresholds for converting the NOS scores to AHRQ quality standards (see Table S5 a)

Figure S8 a: Results of the JBI Checklist for Prevalence Studies Assessment of Eight Non-comparative Cohort Studies



JBI= Johanna Briggs Institute