



# Omalizumab and cancer risk: Current evidence in allergic asthma, chronic urticaria, and chronic rhinosinusitis with nasal polyps

Diego Bagnasco, MD, PhD<sup>a,b\*</sup>, Rikki Frank Canevari, MD<sup>b,c</sup>, Stefano Del Giacco, MD<sup>d</sup>, Silvia Ferrucci, MD<sup>e</sup>, Paolo Pigatto, MD<sup>f</sup>, Paolo Castelnuovo, MD<sup>g</sup>, Gian Luigi Marseglia, MD<sup>h</sup>, Arzu Didem Yalcin, MD<sup>i</sup>, Girolamo Pelaia, MD<sup>j</sup> and Giorgio Walter Canonica, MD<sup>k</sup>

## ABSTRACT

Omalizumab is a biological drug targeting circulating IgE, approved for use in allergic asthma, chronic spontaneous urticaria, and recently for chronic rhinosinusitis with nasal polyps, with good efficacy in all these settings. Some concerns about omalizumab safety have been raised as its use has been recently linked to potential increased cancer risk. Nevertheless, literature evidence does not support this statement, and clinical studies and evidence from real-world registries and surveillance analysis have consistently reported drug safety.

**Keywords:** Severe asthma, Omalizumab, Cancer, Anti IgE, Monoclonal antibodies

Omalizumab, an anti-IgE recombinant humanized monoclonal antibody reducing free IgE in plasma, is indicated, and widely demonstrated to have a proven efficacy, to treat allergic asthma, chronic spontaneous urticaria, and chronic rhinosinusitis with nasal polyps with an overall positive outcome in these settings.<sup>1-3</sup> Omalizumab targets an immune system molecule altering its circulating levels: the close connection between immunological surveillance and cancer development has recently brought to consideration the possible involvement of allergy pathways in tumor progression.<sup>4</sup> Therefore, a careful consideration of the safety

profile of every agent used to dampen and modulate allergic reactions is warranted, given the several immunological pathways potentially influenced by the immune molecule; indeed, omalizumab efficacy and safety have been deeply analyzed through controlled clinical trials, systematic reviews, and observational studies.<sup>3,5-7</sup>

Recently, some concerns have been raised about the long-term safety of omalizumab, particularly its relation to the occurrence of malignancies such as breast cancer and lung cancer but also prostate cancer, colon cancer, malignant melanoma, thyroid cancer, and leukemia,<sup>8</sup> on the rationale of the possible existing link between low IgE levels detected in cancer patients.<sup>9</sup>

However, this evidence does not appear to be supported by available data in the literature, in any of the approved settings of use. Indeed, we searched Pubmed for peer-reviewed studies in English, with the keywords "Omalizumab" AND ("allergic asthma" OR "chronic spontaneous urticaria" OR "chronic rhinosinusitis with nasal polyps"), aiming to look for indications about the potential increased cancer risk associated to the treatment.

<sup>a</sup>Allergy and Respiratory Diseases, Department of Internal Medicine (DIMI), University of Genoa, Italy

\*Corresponding author. Allergy and Respiratory Diseases, IRCCS San Martino, University of Genoa, Genoa, Italy. E-mail: [diego.bagnasco@dimi.unige.it](mailto:diego.bagnasco@dimi.unige.it)

Full list of author information is available at the end of the article

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In asthma patients, the use of omalizumab is not associated with increased cancer risk and its safety profile is supported by several studies. The EXCELS study, a prospective cohort study performed in a real-world setting, observed patients with moderate to severe asthma over a period of 5 years.<sup>5</sup> There was no difference in the increase of malignancies between the omalizumab-treated group and the non-omalizumab-treated individuals, with both the overall frequency and the frequency of different cancer types being similar to those reported for the general population. The risk of malignancy upon omalizumab treatment was also evaluated in a large aggregate analysis, including data from 67 randomized, double-blind, placebo-controlled trials from phase I to IV (for a total of 11 459 asthmatic subjects), which allowed to observe the effects of the drug on 7789 patients compared to the control arm. The analysis showed that 14/4254 (0.32%) of patients treated with omalizumab and 11/3178 (0.34%) enrolled in the placebo arm developed malignancy, leading to an observed cancer incidence rate of 4.14 (95% CI, 2.26–6.94) and 4.45 (95% CI, 2.22–7.94) per 1000 person-year, for omalizumab and placebo groups, respectively. Therefore, no association between treatment with omalizumab and the risk of malignancy was demonstrated in randomized, double-blind, placebo-controlled studies.<sup>10</sup> In addition, a post-marketing observational surveillance trial involving 30 certified Spanish centers, with patients under more than 2 years of treatment with omalizumab in a real-life setting, identified arthralgia and headache as the most common adverse events.<sup>6</sup> Moreover, a recent observation from the Danish National Patient Registry, which included data from 1444 subjects treated with omalizumab for more than 2 years for either asthma or chronic urticaria<sup>11</sup> did not reveal any increased incidence of tumors, and so did a real-life study with a 9-year follow-up including 91 patients.<sup>1</sup>

Likewise, the incidence of adverse effects in patients with urticaria upon omalizumab treatment was analyzed in 2 systematic reviews<sup>2,12</sup> and 1 real-world data study<sup>7</sup> and either no or mild (headache, fatigue, injection site reaction) adverse events were reported. A meta-analysis performed on patients treated for idiopathic urticaria or allergic asthma confirmed, once again,

that there was no significant increase in solid epithelial cancer in patients treated with omalizumab (Peto OR: 0.65, 95% CI: 0.11, 3.74,  $I^2 = 41\%$ ), in both respiratory and dermatological diseases.<sup>13</sup>

Omalizumab has been recently approved to treat chronic rhinosinusitis with nasal polyps.<sup>14</sup> Its efficacy and safety in this setting have been analyzed in a systematic review and meta-analysis of randomized controlled trials<sup>3</sup> showing no difference in the risk of adverse events or serious adverse events. However, no specific indication about cancer risk is reported as the studies included in the meta-analysis are too short in follow-up to evaluate late-onset adverse events such as cancer properly.

In light of what is reported here, the hypothesis of an increased risk of malignancy upon omalizumab use is not confirmed. The disproportionality analysis reported in the study of Mota et al suggests that omalizumab may have an elevated risk of malignancy, a concept which has to be further proven by clinical investigations, as stated by the authors themselves.<sup>8</sup> It is crucial to clarify and analyze the above mentioned message. It is important to point out that statistical methodology of proportionality and disproportionality is, simply, a numerical statistical analysis and, as such, requires quality control of data collection and, above all, a careful clinical evaluation in order to assess the true weight of the data. In fact “statistical signal” alone can be regarded as a “potential signal” related to the safety of a medicinal product, but needs clinical and scientific data to be confirmed. With regard to the report on omalizumab, the clinical data reported above and below do not confirm what emerged from the statistical analysis by Mota.

The literature-reported long-term studies described here highlight instead a full safety profile of the drug (Table 1). Available data summarized here add to the completeness of the US Food and Drug Administration (FDA) 2014 statement,<sup>15</sup> reporting the usefulness of extending pharmacovigilance studies to confirm the absence of a neoplastic risk for patients undergoing treatment with omalizumab.

The present analysis underlines that there is no documented increased carcinogenic risk in long-term treated patients. The data collection needed to support omalizumab safety in terms of

Disease	Reference	Year	Objective of the trial	Evaluated Sample	Effect on malignancy
ASTHMA	Rodrigo GJ et al. Chest. 2011; 139(1):28-35	2011	Establish the efficacy and safety of subcutaneous OMA as add-on therapy to corticosteroids	3429 patients in 8 studies. Systematic review of placebo-controlled studies	No increased risk of malignancy
ASTHMA	Tzortzaki EG et al. Pulm Pharmacol Ther. 2012; 25(1):77-82	2011	Evaluate the 4 months, 1- and 4-year effectiveness of OMA treatment, in a non-interventional, observational "real-life" study	60 patients with severe persistent allergic asthma	-
ASTHMA	Vennera MDC et al. Spanish Registry. J Asthma. 2012; 49(4):416-22	2012	Evaluate the efficacy and tolerability of OMA in a real-life setting in Spain, particularly in those patients with immunoglobulin E (IgE) levels out of range. Follow-up time- 2 years	266 uncontrolled severe asthma patients receiving high-dose inhaled corticosteroids plus long-acting $\beta$ 2-agonist were recruited	-
ASTHMA	Busse W et al. J Allergy Clin Immunol. 2012; 129(4):983-9.e6	2012	Examine the incidence of malignancy using comprehensive pooled data from clinical trials of OMA-treated patients	11,459 patients in 67 phase I to IV clinical trials	25 patients with malignancy in RDBPC trials: 14/4254 (0.33%) treated with OMA 11/3178 (0.35%) treated with placebo Incidence rates per 1000 patient-years of observation time for OMA- and placebo-treated patients were 4.14 (95% CI, 2.26-6.94) and 4.45 (95% CI, 2.22-7.94)
ASTHMA	Long A et al. J Allergy Clin Immunol. 2014; 134(3):560-567.e4	2014	Evaluate long-term safety in OMA-treated and non-OMA-treated patients	4393 patients (>12 years of age) with moderate-to-severe allergic asthma in a	No increased risk of malignancy

(continued)

Disease	Reference	Year	Objective of the trial	Evaluated Sample	Effect on malignancy
				prospective observational cohort study	
ASTHMA	Li J et al. <i>J Allergy Clin Immunol.</i> 2015; 135(1):289	2015	Highlight on malignancy in EXCELS study		No increased risk of malignancy
ASTHMA	Rodrigo GJ et al. <i>Pediatr Allergy Immunol.</i> 2015; 26(6):551-6	2015	Establish the efficacy and safety of subcutaneous OMA as an add-on therapy	1381 patients in three randomized controlled trials	No increased risk of malignancy
ASTHMA	Di Bona D et al. <i>Respir Med.</i> 2017; 130:55-60	2017	Assess the safety of OMA in patients under long-term treatment in a real-life setting	91 difficult-to-control asthmatic patients treated with OMA up to 9 years were retrospectively evaluated	No increased risk of malignancy
ASTHMA	Sousa J et al. <i>Expert Opin Drug Saf.</i> 2020; 19(1):99-106	2020	Characterize the safety profile of biologicals used in asthma	Retrospective and descriptive analysis of spontaneous reports involving OMA and mepolizumab, sent to the Portuguese Pharmacovigilance System, since market launch until October 2018	
ASTHMA and URTICARIA	Ali Z et al. <i>Br J Dermatol.</i> 2022; 186(4):746-748	2022	Evaluation of OMA and cancer risk association	1444 patients treated with OMA both for urticaria and asthma	No increased risk of malignancy both in asthma and urticaria
URTICARIA	Metz M et al. <i>Curr Opin Allergy Clin Immunol.</i> 2012; 12(4):406-11	2012	Summarize and discuss all published information on the use of OMA in urticaria	225 patients (209 with asthma and 16 with urticaria)	-
URTICARIA	Kaplan A et al. <i>J Allergy Clin Immunol.</i> 2013; 132(1):101-9	2013	To evaluate the safety and efficacy of 24-week treatment with OMA in patients with persistent CIU/CSU	336 patients enrolled in a phase III study, on a 16 week period of observation	No increased risk of malignancy

(continued)

Disease	Reference	Year	Objective of the trial	Evaluated Sample	Effect on malignancy
URTICARIA	Chicharro P et al. <i>Actas Dermosifiliogr.</i> 2017; 108(5):423-431	2016	Analyze the most important aspects of the cases and the outcomes reported	This review brings together case reports and case series describing the use of OMA to treat chronic inducible urticaria	-
URTICARIA	Tharp MD et al. <i>JAMA Dermatol.</i> 2019; 155(1):29-38	2018	Analyze benefits and harms of OMA in the real-world clinical management of CIU regarding urticaria activity, treatment response, and adverse events	294 patients described in observational studies (January 1, 2006, to January 1, 2018) and scientific abstracts on the effectiveness of OMA in CIU	-
URTICARIA	Bernstein JA et al. <i>Expert Opin Biol Ther.</i> 2018; 18(4):425-448	2018	Provide a synthesis of evidence and opinion on the use of OMA across the diverse patient phenotypes affected by CIU/CSU.	Review of 84 observational effectiveness studies covers treatments (dosing, medication use), clinical outcomes (treatment response, disease activity, quality of life), and safety	-
URTICARIA	Maurer M et al. <i>J Allergy Clin Immunol.</i> 2018; 141(2):638-649	2018	Determine the strength of evidence for OMA efficacy and safety in the treatment of chronic inducible urticarias, symptomatic dermographism, cold urticaria, delayed-pressure urticaria, solar urticaria, heat urticaria, vibratory angioedema, cholinergic urticaria, contact urticaria, and aquagenic urticaria	Systematic review of 43 trials, case studies, case reports, and analyses	-

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Disease	Reference	Year	Objective of the trial	Evaluated Sample	Effect on malignancy
URTICARIA and Athopic Asthma	Johnston A et al. <i>Clin Exp Allergy</i> . 2019; 49(10):1291-1305	2019	Investigate whether prolonged treatment with OMA influences development or progression of solid epithelial cancer in patients with atopic asthma or CIU	11,758 patients from 12 studies in a systematic review and meta-analysis of intervention and observational studies	No increased risk of malignancy between patients treated with OMA compared to standard of care (Peto OR: 0.65, 95% CI: 0.11, 3.74, I <sup>2</sup> = 41%). In comparative study, the risk of solid epithelial tumor was OMA: 2.3%, standard of care: 2.2%, p = N.S.
URTICARIA	Metz M et al. <i>Clin Rev Allergy Immunol</i> . 2020; 59(1):38-45.	2020	Provide an overview of studies and the real-world data on OMA up-dosing as it became necessary to obtain complete CSU symptom control in a proportion of patients.	1207 patients from observational studies (from June 2003 to October 2019) on the up-dosing of OMA in CSU	-
URTICARIA	Agache J et al. <i>Allergy</i> . 2021; 76(1):59-70	2021	Evaluate the efficacy and safety of OMA for CSU	2126 patients in 11 randomized controlled trials	-
RHYNOSINUSITIS	Gevaert P et al. <i>J Allergy Clin Immunol</i> . 2020; 146(3):595-605	2019	Determine OMA safety/efficacy in CRSwNP in phase III trials (POLYP 1, POLYP 2).	265 adults with CRSwNP and with an inadequate response to intranasal corticosteroids were randomized (1:1) to OMA or placebo and intranasal mometasone for 24 weeks	-
RHYNOSINUSITIS	Chong LY et al. <i>Cochrane Database Syst Rev</i> . 2020; 2(2):CD013513	2020	Assess the effects of biologics for the treatment of chronic rhinosinusitis	1262 patients analyzed by a Cochrane ENT Information Specialist	-

(continued)

Disease	Reference	Year	Objective of the trial	Evaluated Sample	Effect on malignancy
RHYNOSINUSITIS	Wu Q et al. <i>BMJ Open</i> . 2021; 11(9):e047344	2021	Assess the efficacy and safety of OMA for CRSwNP	302 patients from 3 trials in a meta-analyses	-
RHYNOSINUSITIS	Agache J et al. <i>Allergy</i> . 2021; 76(8):2337-2353	2021	Evaluate the efficacy and safety of biologicals for CRSwNP, compared with the standard of care	Systemic review of 303 patients treated with OMA	-

**Table 1.** (Continued) Record of malignancy in trials about Omalizumab in asthma, urticaria and chronic rhinosinusitis. OMA: omalizumab; RDBPC: randomized double-blind placebo-controlled; CIU: chronic idiopathic urticaria; CSU: chronic spontaneous urticaria; CRSwNP: chronic rhinosinusitis with nasal polyposis

cancer risk has required the pooling of studies with long-term follow-up, in some cases involving a small number of patients. In the future, the exponential development of national and international registries related to different diseases will allow performing similar analysis more simply and efficiently. Besides the collection of clinical data from patients' long-term follow-up, specific evidence, at the molecular level, should be provided to properly link omalizumab-induced reduction of IgE to mechanisms sustaining cancer development. Furthermore, there is no evidence that omalizumab lowers IgE to the extremely low levels observed in some cancer patients, for whom this reduction could be secondary to an alteration of the immune system related to the malignancy itself. More insights on the involvement on serum IgE on cancer progression may come from a phase I ongoing clinical trial, testing the role of an IgE antibody therapy in solid cancers (NCT02546921).

In conclusion, although the development of tumors in some omalizumab treated patients has been discussed, both systematic studies and meta-analyses performed on more than 40 000 patients have not found an increased number of tumor cases compared to the general population.

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#### Author contribution

All the authors analyzed the literature, drafted, revised and approved the final version of the manuscript.

#### Ethics approval

Not applicable.

#### Declaration of competing interest

The authors report no competing interests.

#### Author details

<sup>a</sup>Allergy and Respiratory Diseases, Department of Internal Medicine (DIMI), University of Genoa, Italy. <sup>b</sup>IRCCS Policlinico San Martino, Genoa, Italy. <sup>c</sup>Unit of Otorhinolaryngology-Head and Neck Surgery, University of Genoa, Genoa, Italy. <sup>d</sup>Department of Medical Sciences and Public Health, University of Cagliari, Cagliari, Italy. <sup>e</sup>Department of Clinical Sciences and Community Health, University of Milan, Milan, Italy. <sup>f</sup>Clinical Dermatology, IRCCS Istituto Ortopedico Galeazzi, Milan, Italy. <sup>g</sup>Division of Otorhinolaryngology, Department of Biotechnology and Life Sciences, University of Insubria, Ospedale di Circolo e Fondazione Macchi, Varese, Italy. <sup>h</sup>Pediatric Clinic, Fondazione IRCCS Policlinico "S. Matteo," University of Pavia, Pavia, Italy. <sup>i</sup>Division of Allergy and Immunology, Department of Internal Medicine, Antalya Education and Research Hospital, University of Health Sciences, Antalya, Turkey. <sup>j</sup>Department of Health Sciences, Magna Graecia University, Catanzaro, Italy. <sup>k</sup>Personalized Medicine Center, Asthma and Allergy, Humanitas Clinical and Research Center, IRCCS, Rozzano, Milan, Italy.

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