

# Omalizumab for treatment of chronic urticaria: A review of effective dose

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## ABSTRACT

Omalizumab (Xolair®), a humanized anti-IgE monoclonal antibody, is effective and well-tolerated in patients with chronic spontaneous urticaria refractory to H<sub>1</sub> antihistamines. The aim of this review was to present the effective dose of omalizumab for urticaria treatment in patients. Several databases, including PubMed, EMBASE, Scopus, Google, SID, Magiran, and Irandoc, were selected. The search process was performed using the keywords of Xolair, omalizumab, urticaria, chronic urticaria, effect, and treatment. Sixty related articles were found. All studies have been conducted on people over 12 years of age with the exception of 2 articles investigating patients over 7 years old. Most studies have been performed on patients within the age range of 12-75 years and the maximum age of 81 years. Omalizumab has been administered at different doses for patients with chronic urticaria (75-600 mg). Omalizumab has shown a treatment effect at all administered doses; however, it has the greatest effect when administered at the dose of 300 mg. The interval of subcutaneous injections was 2-6 weeks. In conclusion, the administration of omalizumab is effective at doses of 150 and 300 mg although the most effective dose is 300 mg.

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## Introduction

Urticaria is a transient skin disorder characterized by pruritic wheal and flare lesions, which subsides within 24 h. Acute urticaria has a duration less than 6 weeks. On the other hand, chronic urticaria continues on most days of the week for more than 6 weeks, and is less common (0.1-1%) than acute urticarial (15-25%) in general population. Overall, about 20% of people in the community experience urticaria during their lives and 20-30% of chronic urticaria is physical urticaria (e.g., heat, cholinergic, cold, vibration, pressure, sunlight, and exercise) (1-3). Chronic urticaria is more common in adults than children among whom women are affected twice more than men. Angioedema, the swelling of the deep dermis and subcutaneous associated with pain and burning rather than itching, is observed in 30-50% of patients with urticaria.

The etiology of chronic urticaria is not detectable in the majority of cases; in this regard, they are mostly recognized as idiopathic chronic urticaria (ICU). Some cases are autoimmune urticaria (about 30% of urticaria) that produce anti-IgG antibodies against high-affinity IgE receptor (FceRI) on mast cells and basophils, directly against IgE antibodies (1, 2), or by known autoimmune disorders, such as autoimmune thyroiditis (4, 5). Different genotypes involved in urticarial cause various phenotypes. The promoter polymorphism of TGF-Beta1 gene-509C>T may be involved in ICU (6). The causes of urticaria in children are less unknown than those of adults (7). Urticaria, in addition to itching, affects the quality of people's lives. It also imposes a financial burden on the family and the

country. Our previous study showed that some aspects of patients' life quality are affected by this disease (8). Acute urticaria is usually self-limiting, and in most cases it does not need any evaluation. Food, drug, and stings can induce acute urticaria (usually IgE mediated). Nonspecific agents, inducing acute urticarial, includes radio contrast media, viral infections, opiate derived medications, non-steroidal anti-inflammatory drugs (NSAIDs), and Angiotensin-converting enzyme inhibitors (ACEIs). The remission rate of chronic urticaria is 65% within 3 years, 85% within 5 years and 98% within 10 years (1-5). Some of patients with chronic spontaneous urticaria report systemic manifestations, such as headache, fatigue, pain or swelling of joints, wheezing, flushing, gastrointestinal symptoms, and palpitations. The diagnosis of urticaria based on clinical manifestations and physical examination. General and routine tests are not recommended for the diagnosis of urticarial. However, the initial tests performed for spontaneous chronic urticaria include a complete blood count with differential, C-reactive protein or erythrocyte sedimentation rate, thyroid stimulating hormone, activities of aspartate transaminase, alanine transaminase, and urinalysis. Skin biopsy can also be performed to exclude urticarial vasculitis (9, 10).

The identification of the factors causing urticaria is the best preventive measure for this disease. The first line treatment is second-generation antihistamine with standard dosage. In the absence of a response within 2-4 weeks, the dosage of the drug is increased by 2-4 times. In case of the lack of a response, such drugs as

second generation anti-histamines or H2 blockers anti-histamines or leukotriene antagonists or first-generation antihistamines and or Omalizumab can be added to the regimen. Finally, immunosuppressive drugs (e.g., cyclosporine) are used in the absence of response to the previous drugs. For patients with anaphylaxis, epinephrine is usually recommended (7, 11, 12).

Omalizumab (tradename as Xolair®; Manufactured by Genentech, Inc: USA) is a recombinant humanized monoclonal antibody bind to free IgE; however, it does not bind to the FcεRI receptors or receptor-bound IgE. It is approved for the treatment of refractory chronic spontaneous urticaria as third-line therapy. Xolair® is recommended for use in people over 12 years of age. Recently, the drug has been prescribed for children with the age range of 6-12 years (11, 12). Omalizumab, which is used subcutaneously every 2-4 weeks, leads to various results at different doses (75, 150, and ≥300mg) regarding the treatment of chronic urticaria (1, 10, 11, 13).

Nasopharyngitis, sinusitis, upper respiratory tract infection, viral upper respiratory tract infection, headache, and cough are the most common side effects of Omalizumab. Anaphylaxis is the rare side effect of Omalizumab. Regarding the injection of the drug, the patient is monitored for 2 h in the first three times of drug administration and then for 30 min from the fourth time onwards (14).

Immunosuppressive drugs, such as corticosteroids, azathioprine, or cyclosporine A, should be reserved for the severe recalcitrant disease. Urticaria measurement tools that can be used for defining response are the urticaria activity score (UAS7) and urticaria control test (UCT) (15-19). This review aimed to find the most effective dose of omalizumab in chronic urticaria.

## Materials and methods

To conduct a narrative review of omalizumab therapy in chronic urticaria, the databases of PubMed, EMBASE, Scopus, Google, SID, Magiran, Irandoc, were searched with keywords of Xolair®, omalizumab, urticaria, chronic urticaria, effect, and treatment. We searched all the short and full articles that were scheduled to publish until December 2018.

## Results

In this review, 60 articles on the use of omalizumab drug in chronic urticaria were selected for clinical trials. All studies have been conducted on people over 12 years of age except for 2 articles. These 2 papers were conducted on patients within the age range of 7 years old and above. The oldest patient was 81 years old. Most studies were conducted on patients within the age range of 18-75 years (Table 1).

Omalizumab has been administered at different doses for patients with chronic urticaria (75-600 mg). However, the prescribed doses for most cases are 150

and 300 mg. The obtained results indicated that all the administered doses have a positive effect on the patients; however, the greatest effect was achieved at the dose of 300 mg. The medicine has been injected subcutaneously for all cases. The interval between injections varies from 2 to 6 weeks, most often every 4 weeks. In the next stage, the incidence is from 2 and 4 weeks.

## Discussion

Omalizumab is a biological treatment (monoclonal antibody) used for chronic urticaria. This drug has been approved for the treatment of urticaria in patients over 12 years old. However, different doses of this medicine have different effects. The present review showed that doses above 150 mg are more effective. This drug exerts the best effect when administered at a dose of 300 mg every 2-4 weeks. However, given the expense of this drug, it is better to use it at a dose of 300 mg every 4 weeks subcutaneously for 12 weeks. In the same vein, most of the articles in this review used the drug for at least 12 weeks. The EAACI/GA<sup>2</sup>LEN/EDF/WAO guideline recommended 300 mg of omalizumab every 4 weeks as a third-line therapy for patients with urticaria unresponsive to up-dosing of antihistamines (34). Fine et al. reported that 150 mg and 300 mg doses of omalizumab are more effective than 75 mg dose every 4 weeks. It should be noted that omalizumab is classified as a category B drug regarding pregnancy (35). Some studies suggest that the 300 mg of omalizumab and others suggest 150-300 mg in the treatment of chronic urticaria (36). In low-income countries, the recommended dose is 150 mg every 4 weeks by World Allergy Organization (WAO) due to the high price of omalizumab. There is no doubt that the administered dose can be increased by 300 mg if the lower dose is not effective. The duration of urticaria treatment is at least 3 months (28).

Turkish guideline for the treatment of patients with urticaria recommends the administration of 300 mg every 28 days for 6 months. The dose can be increased to 450-600 mg if the response cannot be obtained at the dose of 300 mg. Resistance to omalizumab is when there is no response to the dose of 600 mg over a 3-month period. The administration of drug has been approved for patients older than 7 years old. There is not enough data for the use of omalizumab in pregnant women (37). Australian guidelines recommend administering 300 mg of omalizumab for at least 12 weeks in patients with urticaria when they are not responsive to up-dosing antihistamines (38). In a Brazilian study, the dose of 300 mg was more effective than 150 mg administered every 4 weeks for a 12-week period in patients with urticaria (age range: 16-74 years old). Although a higher dose is more effective, we should individualize the implemented therapy (39). A recent study has also shown that 300 mg dose of omalizumab is effective in adults who do not respond to

**Table 1** Characteristics of clinical trial studies of omalizumab in patients with urticaria

Author (Year)	Dose of omalizumab (mg)	Interval	Age (Year)	Significant dose effectiveness (mg)
Hide <sup>20</sup> (2018)	150, 300	Q 4 weeks (12 weeks)	12-75	300
Hide <sup>21</sup> (2017)	150, 300	Q 4 weeks (12 weeks)	12-75	150, 300
Saini <sup>22</sup> (2015)	75, 150, 300	Q 4 weeks (24 weeks)	12-75	300
Metz <sup>23</sup> (2017)	300	Q 4 weeks (12 weeks)	18-75	300
Kaplan <sup>24</sup> (2013)	300	Q 4 weeks (24 weeks)	18-75	300
Saini <sup>25</sup> (2011)	75, 300, 600	Single dose	12-75	300, 600
Maurer <sup>26</sup> (2011)	75-375	Q 2-4 weeks (24 weeks)	18-70	All doses
Kaplan <sup>27</sup> (2008)	0.016 mg/kg/IU mL (-1) IgE per month (150 mg)	Q 2-4 weeks (16 weeks)	18-75	≥150
Wilches <sup>28</sup> (2016)	150	Q 4 weeks (12 - 20 weeks)	18-81	30-70% effective
Ivyanskiy <sup>1</sup>	150	Q 2 weeks (1-15 months)	15-66	58% effective
Magerl <sup>29</sup>	150-300	2-6 weeks	32-57	300
Clark <sup>30</sup>	300	Q 2-4 weeks	Mean age of 43 years	300 mg q 2 weeks
Bilali <sup>31</sup>		150-450 mg	7-18	
Sussman <sup>32</sup>	150-300	Q 4 weeks (3-5 months)	7-78	69% effective
Finlay <sup>33</sup>	75-300	Q 4 weeks (12-24 weeks)	12-75	300

antihistamine treatment, which was consistent with the findings of most previous studies (40). The obtained results of a large number of studies indicated that omalizumab improves the clinical symptoms and life quality of patients with chronic urticaria (33, 34). Omalizumab is not a medicine with serious side effects; however, some of the reported side effects include headache, asthenia, arthralgia, weight gain, alopecia, nausea, fatigue, diarrhea, abdominal pain and injection site reaction (33-34, 40). Based on the reviewed

studies, there was no report of omalizumab-induced mortality. The recurrence of urticaria occurs at the end of the drug administration period with different percentages requiring the re-administration of the drug. Despite numerous studies, there is no clear indication for the duration of the omalizumab treatment. If the drug is not effective after 6 months, the patient is considered a non-responder and the medication is discontinued (33, 34).

## Conflict of interest

All authors declare no conflicts of interest.

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