Omalizumab for Patients with Severe Allergic Asthma

Subjects: Allergy

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Evidence suggests that omalizumab improves asthma control and reduces the incidence and frequency of exacerbations in patients with severe allergic asthma. Omalizumab is also effective in those patients in reducing corticosteroid use and healthcare utilization, while it also seems to improve lung function. Several biomarkers have been recognized in predicting its efficacy in its target group of patients, while the optimal duration for evaluating its efficacy is between 16 and 32 weeks.

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1. Introduction

Asthma is a heterogeneous disease with different identifiable clusters of demographics, clinical and/or pathophysiological characteristics, often referred to as asthma phenotypes [1]. The most common asthma phenotype is allergic asthma, which counts for up to 80% of childhood asthma and more than 50% of adult asthma cases [2][3]. Nowadays, an improved understanding of the pathophysiology of asthma and the identification of different phenotypes led to the development of personalized, phenotype-guided treatments [4][5][6].

Omalizumab, a recombinant humanized monoclonal antibody which specifically binds to the C epsilon3 domain of immunoglobulin (Ig) E was marketed in the dawn of the 21st century and was the first among many of such treatments [7]. Omalizumab is currently suggested in patients aged six years or older with difficult-to-treat to severe persistent allergic asthma according to the Global Initiative for Asthma (GINA) guidelines, who fulfill one or more of the following criteria: sensitization to inhaled allergen(s) on a skin prick testing or specific IgE.; and body weight within a local dosing range, and more than a specified number of exacerbations within the last year, despite a daily high dose of inhaled corticosteroids, plus a long-acting inhaled beta2-agonist [1][8][9].

2. Omalizumab's Efficacy on Asthma Symptom Improvement

Several tools are available for monitoring asthma control, such as validated questionnaires (asthma control test (ACT) [10], an asthma control questionnaire (ACQ) [11], and an asthma quality of life questionnaire (AQLQ) [12], etc. [10][11][12][13][14][15][16].

Ayres et al. proved that out of a total of 312 patients with poorly controlled, severe, allergic asthma, those who were treated with omalizumab plus the best standard care experienced a significant improvement in asthma

symptom control compared to the control group, where the best standard care was offered (Table S1) [17]. In another randomized controlled trial, which included 400 asthmatic patients, Bousquet et al. demonstrated that asthma control, measured by ACQ score was significantly improved both at 16 and at 32 weeks in patients who received omalizumab compared to controls (Table S1) [18]. Moreover, the results of several early clinical trials [19][20][21][22][23][24], as well as of later ones, [25][26] indicated symptom improvement in asthmatic patients, both children and adults, who received omalizumab, compared to the controls, although those results were not always statistically significant. Nevertheless, a systematic review with meta-analysis which combined these studies concluded that in a total of 3429 participants, asthmatic patients who received omalizumab exhibited a statistically significant improvement not only in asthma control scales but also in quality-of-life scales, such as AQLQ.; compared to the controls [27]. The same findings were also demonstrated by another systematic review with meta-analysis, which included three randomized, double-blind, placebo-controlled studies, that enrolled 1412 patients with moderate or severe allergic asthma [28].

Table S1. Efficacy of omalizumab in patients with severe allergic asthma.

Study	Design	Number of patients	Main outcomes
Busse et al. (2001)	phase III, double-blinded, placebo- controlled trial	525	fewer asthma exacerbations per subject with omalizumab vs placebo (0.28 vs 0.54, p=0.006 during stable steroid phase and 0.39 vs 0.66, p=0,003 during steroid reduction phase)
Solèr et al. (2001)	multi-center, randomized, double-blind, placebo-controlled, parallel-group study	546	omalizumab group vs placebo group: 58% and 525 fewer exacerbations per patients during stable-steroid and steroid-reduction phase (p<0,001), comparable overall incidence of adverse events between groups (p=0,504)
Ayres et al. (2004)	randomized, open-label, multicenter, parallel-group study	312	annualized mean number of asthma- deterioration related incidents/mean exacerbation rates with BSC alone vs with omalizumab: 9.76 vs 4.92 (p<0.001)/ 2.86 vs 1.12 (p<0.001)
Holgate et al. (2004)	meta-analysis of three randomized, double-blind, placebo-controlled studies	1412	mean significant exacerbation rate per patient- year: 1.56 with placebo vs 0.69 with omalizumab, p=0,007, omalizumab vs placebo: improvement from baseline in PEFR (p=0,026), overall AQoL

			(p=0,042), mean nocturnal (p=0,007) and total (p=0,011) asthma symptoms
Humbert et al. (2005)	double-blind, parallel-group, multicenter study	419	omalizumab reduced severe asthma exacerbation rate vs placebo (0.24 vs 0.48,p=0,002) and emergency visit rate (0.24 vs 0.43, p=0,038), omalizumab significantly improved sthma- related quality of life, morning peak expiratory flow and asthma symptom scores
Brusselle et al. (2009)	open-label, multicenter, pharmaco- epidemiologic study	158	>82% improvement in total AQLQ scores of > or = 0.5 points (p<0,001), >91% were exacerbation- free (p<0,001) at 16 weeks vs >84% improvement in total AQLQ scores of > or = 0.5 points (p<0,001), >65% were exacerbation-free (p<0,001) at 52 weeks
Bousquet et al. (2011)	randomized, open-label, multicenter, parallel-group study	400	omalizumab-treated patients: improvement in exacerbation rates (p<0.001), severe exacerbation rates (p<0.05), hospitalizations (p<0.05), total emergency visits (p<0,05), ACQ score (p<0.001)
Barnes et al. (2013)	10-center retrospective observational study	147	34% reduction in total OCS prescription at 12 months, improvement in mean FEV1% at 16 weeks (62,94 vs 70,98, p<0,01), reduction in healthcare utilization at 12 months (p<0,05)
Deschildre et al. (2013)	1-year real life multicenter survey	104	decrease in exacerbations (4.4 to 1.25 per patient after 1 year), decrease in hospitalizations by 88.5%, mean improvement of lung function: 4.9% pred. for FEV1 95% CI, p<0,05) and 9.5% pred. for FEF25-75 (95% CI, p<0,05)
Braunstahl et al. (2013)	international, single-arm, open- label, observational study	943	no clinically significant or severe clinically significant asthma exacerbations higher at 12 months (82.4% and 95.8%) and 24 months (81.9% and 95.6%) vs pre-treatment period (4.9% and 27.4%),

			improvement in activity limitation （41.7%）
			at 24 months vs 46.6% at 12 months, p<0,05) and in rescue medication use (49.8% at 24 months vs 54.1% at 12 months, p<0,05)
Molimard et al. (2014)	observational, descriptive, cross- sectional, retrospective study	61	loss of asthma control in 34 patients (55.7%) with a median interval between discontinuation and loss of control of 13.0 months (mean 20.4 ± 2.6 [95% CI: 8.3-28.1])
Sposato et al. (2016)	multi-center, observational study	105	improvement in ACT values (p<0.001;comparing pre-post) in each group (pre values: 15[IQR:12-18]; 14 [IQR:10-16]; 15 [IQR:12-16]; post-values: 24[IQR:22-25]; 21 [IQR:20-23]; 20 [IQR:18-22]; measured in young, middle-aged and elderly subjects), reduction in exacerbations and ICS treatment after omalizumab in each group (p<0,001)
Iribarren et al. (2017)	observational study	7836	omalizumab-treated patients had a higher rate of CV/CBV serious adverse events (13.4 per 1,000 person years [PYs]) than did non-omalizumab- treated patients (8.1 per 1,000 PYs), ATE rates per 1,000 PYs were 6.66 (101 patients/15,160 PYs) in the omalizumab cohort and 4.64 (46 patients/9,904 PYs) in the non-omalizumab cohort
Ke et al. (2018)	retrospective observational cohort study	1564	asthma-related medication use decreased from the preindex to the postindex periods (oral corticosteroids, p < 0.001; ICSs, p< 0.001; LABAs, p = 0.009; ICS-LABA combination, p<0.001; leukotriene modifiers, p< 0.001), the proportion of patients with any asthma exacerbations decreased by 33.6% (p< 0.001)
Al-Ahmad et al. (2018)	4-year observational study	65	ICS/LABA dose significantly reduced from 65 (100%) to 25

			(38.5%) after 4 years of treatment (p < 0.001); ACT scores significantly increased from 15 ± 3 at baseline to 23 ± 3 (p < 0.001) and FEV1 level from 55.6 ± 10.6 to 76.63 ± 10.34 at year 4
Oliveira et al. (2018)	non-interventional, prospective study	32	at 12 months of omalizumab: improvement in BMI, number of exacerbations, rescue medication, disease control and lung function(p<0,05)

Apart from clinical trials, there are also several observational, every-day clinical practice studies which also evaluated the efficacy of omalizumab in asthma symptom control. Barnes et al. demonstrated that both asthma control, measured by ACT and quality of life, measured by AQLQ.; were significantly improved in asthmatic patients after the initiation of omalizumab both at 16 and at 52 weeks [29]. Similar results were also published by Deschildre et al., who used GINA criteria to assess asthma control in children with asthma after the initiation of omalizumab (Table S1) [30]. Researchers found that the initiation of omalizumab in patients with severe allergic asthma led to a significant improvement in both daily and nightly symptoms as well as in different asthma symptom scales such as AQLQ.; mini-AQLQ and ACT [31][32][33]. On the other hand, Nopp et al., in a very small-scale study, reported that 8 out of 18 asthmatic patients who were treated with omalizumab for 6 months still exhibited asthma symptom improvement 3 years after the discontinuation of omalizumab [34]. However, another study which included 943 patients with asthma reported a significant reduction in (a) daily symptoms, (b) activity limitation, (c) night symptoms, (d) night awakenings due to asthma and (e) the need for reliever medication, after the initiation of omalizumab both at 12 and at 24 months. In the same study, the findings from both ACT and ACQ scales were also significantly improved [34][35].

3. Effectiveness of Omalizumab in Reducing Corticosteroid Use

Alongside standard treatment with ICS.; patients often need to be treated with oral corticosteroids (OCS) to achieve better asthma control [35][36][37][38][39][40][41][42][43][44]. Novel therapy strategies aim to reduce the use of corticosteroids to eliminate possible adverse effects [45][46][47][48][49][50][51][52][53].

Busse et al. found that ICS administration was reduced by 75% in patients with severe asthma 28 weeks after the initiation of omalizumab, which was significantly greater than the 50% reduction in the control group (Table S1) [24]. Similar results about ICS reduction were also reported by another clinical trial at 32 weeks after omalizumab initiation (57.2% of the patients who received omalizumab vs. 43.3% of the placebo group, $p < 0.05$) [21]. Moreover, the effect of omalizumab on ICS reduction was predicted by the Archimedes asthma model for US patients aged 12 and older with moderate-to-severe persistent allergic asthma [54][55][56][57][58]. Apart from ICS dosage reduction,

omalizumab seems to be even more effective in OCS dosage reduction and/or discontinuation [56][59][60][61][62][63]. The beforementioned effects of omalizumab in corticosteroid use have also been confirmed by four systematic reviews with meta-analyses [8][27][64][65].

In addition to clinical trials, the impact of omalizumab on corticosteroids use in severe allergic asthma has also been demonstrated by several observational real-life studies. The initiation of omalizumab resulted in significant reduction in ICS dosage in several studies [30][32][33][66][67], while in another study, its discontinuation led to a significant increase in prescribed ICS dosage [34]. Furthermore, the initiation of omalizumab had the same effect in OCS usage, as it led to significant OCS dosage reduction or discontinuation in several studies [29][35][68][69][70][71][72], while in another study both ICS and OCS reduction was observed in patients with severe allergic asthma who were treated with omalizumab for seven years [73].

4. Efficacy of Omalizumab in Reducing the Rate of Asthma Exacerbations

Severe exacerbations may occur even in patients with mild or well-controlled asthma symptoms as a patient's risk of exacerbations may be independent of the level of symptom control [73][74][75]. More importantly, exacerbations were proved fatal on many occasions [76][77][78][79][80]. Therefore, a successful therapeutic strategy should prevent asthma exacerbations.

Omalizumab resulted in the reduction of the asthma exacerbation rate in numerous clinical trials during the last two decades, both in adults and in children [17][18][19][20][21][22][23][24][25][26][55][60][81][82][83][84]. In two clinical trials, the exacerbation rate was significantly reduced in the omalizumab group (between 35–45% reduction) compared to the control group [18][21]. Ayres et al. reported 1.12 exacerbations per patient per year in the omalizumab group, which was significantly lower than the 2.86 exacerbations per patient per year in the control group (Table S1) [17]. Solèr et al., in one of the first clinical trials of omalizumab which included 546 participants, reported that both the number of exacerbations per patient during the stable-steroid phase (0.28 in the group who received omalizumab vs. 0.66 in the placebo group) as well as during the steroid-reduction phase (0.36 in the group who received omalizumab vs. 0.75 in the placebo group) and the number of patients needed to treat in order to avoid an exacerbation were significantly lower in the omalizumab group compared to the control group (35 in the group who received omalizumab vs. 83 in the placebo group during the steroid-reduction phase/43 in the group who received omalizumab vs. 81 in the placebo group during the steroid-reduction phase) (Table S1) [22]. On the other hand, there are also clinical trials in which the asthma exacerbation rate was not significantly reduced in the omalizumab group compared to the control group [57][85][86]. However, several systematic reviews with meta-analyses have concluded that omalizumab significantly reduces the asthma exacerbation rate compared to a placebo [27][28][64][87]. Moreover, another randomized controlled trial has proved that omalizumab is more effective in preventing asthma exacerbations in fall compared to an inhaled corticosteroid boost [88].

Apart from clinical trials, omalizumab has also been shown to be effective in the reduction of the asthma exacerbation rate in numerous observational real-life studies [29][30][31][32][33][34][35][66][68][73][89][90][91][92][93][94][95][96][97]

[98]. Barnes et al. and Deschildre et al. reported a significant reduction in asthma exacerbations after the initiation of omalizumab from 3.67 to 1.70 per patient per year and from 4.40 to 1.25 per patient per year, respectively (Table S1) [29][30]. Two more studies reported a significant reduction in asthma exacerbations per patient per year after the initiation of omalizumab (from 5.00 to 0.63 and from 5.70 to 1.90, respectively) [32][68]. Three more studies reported a significant reduction in the asthma exacerbation rate between 62% and 82% [31][33][66]. Nopp et al. found that 16 out of 18 patients who discontinued omalizumab still had fewer exacerbations during nights, even 3 years after the drug withdrawal [34]. The effect of omalizumab's discontinuation on the increase of exacerbations was confirmed by two recently published studies [99][100].

5. Omalizumab's Efficacy on Healthcare Utilization

Omalizumab has been shown to be effective in reducing the rate of emergency care visits and hospitalizations [77][79][101][102][103][104][105][106][107][108][109][110][111][112][113][114]. A clinical trial reported that patients treated with omalizumab suffered from 4.92 of such events per year compared to the 9.76 of such events per year in the control group [17]. Humbert et al. showed that, at 28 weeks, omalizumab significantly reduced emergency care visits and hospitalizations compared to the control group (0.24 vs. 0.43 and 0.125 vs. 0.25, respectively) [19]. Moreover, Bousquet et al. have proved a significant reduction in emergency care visits by 60% and in hospitalizations by 67% in the omalizumab group compared to the control group [18].

Real-life studies have demonstrated a significant reduction in emergency care visits and hospitalizations after the initiation of omalizumab which varied between 51–90.8% and 28–95%, respectively [30][31][56][66][115][116][117]. Other studies also reported a significant reduction in hospitalizations from 1.07–5.93 per patient per year to 0.10–2.75 per patient per year and in emergency care visits from 1.13–1.52 per patient per year to 0.29–0.46 per patient per year after the initiation of omalizumab [29][61][96]. Furthermore, Braunstahl et al., in the context of "eXpeRience registry", which included 943 patients with asthma, reported a reduction in the unscheduled asthma-related visits in a healthcare provider from 6.2 per patient per year to 1.0 per patient per year and to 0.5 per patient per year at 12 and 24 months, respectively (Table S1) [35]. Other studies have demonstrated that after four-to-five years from the initiation of omalizumab almost no patient needed an asthma-related hospitalization [32][94][117], while Molimard et al. reported that the reduction in emergency care visits and hospitalizations after the initiation of omalizumab is irrespective of the reduction or the cessation of corticosteroids (Table S1) [68]. In addition to hospital admission, omalizumab also appears to significantly reduce the duration of hospitalization and the cost per hospital stay [118][119][120].

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