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Observational study in severe asthmatic patients after discontinuation of omalizumab for good asthma control

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Received 18 October 2013; accepted 3 February 2014

KEYWORDS

Omalizumab;
Discontinuation;
Asthma control;
Duration of treatment

Summary

Introduction: Severe persistent asthma represents a major and costly public health issue. There is evidence that long-term treatment with omalizumab might have disease-modifying activity but data on the consequences of discontinuing treatment after a positive response are limited. The purpose of this study was to investigate—in real-life prescribing conditions—what happens when omalizumab is discontinued in patients with severe, persistent allergic asthma who have responded well to omalizumab treatment.

Methods: An observational, descriptive, cross-sectional, retrospective study to establish the time to loss of asthma control after the discontinuation of courses of omalizumab treatment of varying duration.

Results: 24 lung specialists reviewed data from 61 responder patients who had discontinued omalizumab after a mean duration of 22.7 ± 13.1 [range: 2.5; 59.5] months of treatment. Loss of asthma control was documented 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]). No correlation was detected between time to loss of control and duration of treatment, although control tended to be sustained for longer in patients whose response had been classified as “excellent” as opposed to “good” (median: 17.0 vs. 12.8 months; NS).

Discussion: The discontinuation of omalizumab was not associated with any rebound effect or exacerbation of the disease, and control was sustained throughout the follow-up period of at least 6 months in nearly half of all patients, including all of those who had been treated for 3.5 years or more. After the reintroduction of omalizumab, 4 out of 20 patients did not respond again.

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Abbreviations: GINA, global initiative for asthma; IgE, immunoglobulin E; FcεRI, high-affinity IgE receptor; BMI, body mass index; FEV₁, forced expiratory volume (1 s); ICS, inhaled corticosteroid; OCS, oral corticosteroid.

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<http://dx.doi.org/10.1016/j.rmed.2014.02.003>

Please cite this article in press as: Molimard M, et al., Observational study in severe asthmatic patients after discontinuation of omalizumab for good asthma control, Respiratory Medicine (2014), <http://dx.doi.org/10.1016/j.rmed.2014.02.003>

Introduction

Asthma remains a major public health problem and a significant proportion of patients have severe, persistent disease that is refractory to continuous treatment, even with a combination of high-dose inhaled corticosteroids and long-acting β_2 -agonists [1]. Although this difficult-to-treat population represents about 5% of all asthma patients, it accounts for over half of the high cost of asthmatic disease to society [2].

Omalizumab, introduced in the United States in 2003 and in Europe in 2005, has been shown to be highly effective at preventing clinically significant asthma exacerbations and reducing steroid requirements in patients with severe, persistent allergic asthma [3–7], notably in those in whom best-available treatment has proven inadequate [8–10] and those at greatest risk of serious morbidity or death [11]. Omalizumab has also been shown to reduce symptoms, improve lung function and improve asthma-related quality of life, and to have a good tolerability profile [reviewed in Ref. [12]].

Omalizumab is a recombinant humanised monoclonal antibody directed against an epitope on the immunoglobulin E molecule (IgE). Binding of omalizumab to IgE blocks its interaction with the high-affinity IgE receptor (Fc ϵ RI), which is found on mast cells, basophils and dendritic cells, and which takes part in Th2 immune response. Treatment with omalizumab has been shown to down-regulate Fc ϵ RI expression on blood basophils and plasmacytoid dendritic cells in patients with severe allergic asthma [13], which might indicate long-term disease-modifying potential.

By June 2013, omalizumab treatment had been initiated in more than 6000 patients in France. The prescribing information for omalizumab stipulates that it is “intended for long-term treatment”, and recommends an evaluation of treatment effectiveness after 16 weeks to decide whether or not to continue. However, no guidance is given on when to discontinue treatment in a responding patient, because, to date, there have been no data from appropriately designed clinical trials that would inform such guidance. Most studies of omalizumab have so far focused on its short- to medium-term clinical effects, but some biological observations, such as Fc ϵ RI down-regulation [13], suggest that omalizumab may have disease-modifying activity if treatment is continued for long enough.

The purpose of this study was to investigate, retrospectively, the clinical effects of omalizumab discontinuation in a real-life population of patients with severe, persistent, allergic asthma whose physician had decided to stop treatment because of good asthma control.

Methods

This was a multicentre, descriptive, observational, retrospective study conducted at 24 centres in France. The objective of the study was to establish—in a real-life population of patients with severe, refractory, allergic asthma who had been successfully treated with omalizumab—the time to loss of asthma control after discontinuation of the drug. Omalizumab had been effective at establishing control of the asthma in all of these patients. Good asthma

control was based on physicians judgement, who took into account the absence of exacerbation and OCS use and the improvement in symptoms, rescue medication use and/or lung function. Subsequent loss of control was defined as one of the following: (i) an exacerbation requiring treatment with an oral corticosteroid (OCS), with failure to re-establish control within 1 month after the last dose of OCS; (ii) two exacerbations requiring OCS treatment within 1 year; or (iii) the persistence of guideline-based criteria of poor control [at least 3 GINA criteria and/or an increase in Asthma Control Questionnaire (ACQ) score of over 1.5 and/or an Asthma Control Test (ACT) score of 19 or less] for over a month.

For this cross-sectional, retrospective study, a randomly selected sample of French lung specialists who had prescribed omalizumab were asked to identify all patients of any age and either gender who had been successfully treated (i.e. resulting in establishment of control of the disease) with a stable dosage of omalizumab for severe, persistent, allergic asthma, whose medical records showed either loss of control at some point after the discontinuation of omalizumab or at least 6 months of sustained control post-withdrawal.

Data were collected from patients' medical records between the beginning of May and the end of October 2011. To establish how omalizumab is used in everyday practice, patients' characteristics were reviewed together with details of omalizumab treatment. Demographic details (date of birth, gender, weight, height and BMI) and baseline asthma characteristics (asthma history, total IgE level, forced expiratory volume measurements (FEV₁) and maintenance asthma treatments) were recorded during omalizumab treatment. Omalizumab dosage and treatment duration were analysed. Physicians were asked to provide data recorded at the date of discontinuation: bodyweight, FEV₁ and maintenance asthma treatments, duration of satisfactory asthma control, date of the last exacerbation requiring treatment with an OCS, control criteria used to make the decision to discontinue omalizumab, and a subjective estimate of the global effectiveness of the course of omalizumab treatment in each case (“good” or “excellent”). After discontinuation, the date of loss of control, and the criterion or criteria used to define loss of control, were recorded. If a patient was restarted on omalizumab, the physician was asked to provide an estimate of the global effectiveness of the follow-up course.

Statistics

An analysis population was defined, based on main inclusion/exclusion criteria and minimum follow-up duration availability. Quantitative variables were expressed as mean and standard deviation, or median and 95% confidence intervals. Qualitative variables were expressed as number of patients and percentage. Missing data are indicated. Time to loss of control was calculated using the Kaplan–Meier method. Certain analyses were performed on sub-groups stratified according to the physician's estimate of the global effectiveness of omalizumab treatment and the length of the course of omalizumab treatment (<1 year, 1–2 years and >2 years).

Results

Patients

A total of 73 patients were identified by 24 physicians. Twelve of these patients were excluded from the analysis population, the main reasons being need for OCS at the time of discontinuation (6 patients) – a patient who still requires continuous OCS treatment cannot be considered as well controlled – insufficient follow-up time in patients in whom loss of control was not documented (2 patients), and no details on control (2 patients). Therefore, the study population comprised 61 patients.

Characteristics at the time of omalizumab initiation

Baseline characteristics are shown in Table 1. Patients were between 6 and 82 years of age (mean 41 years; eight between 6 and 11 years and six between 12 and 17 years), and nearly two-thirds were women. All had longstanding severe asthma (mean duration: 22.3 ± 15.7 years) with constitutively impaired respiratory function (mean FEV₁ 72% of the predicted value). Mean IgE level was 544 ± 844 IU/mL. All patients except one were taking an inhaled corticosteroid (ICS; 50% fluticasone, 40% budesonide and 10% beclomethasone), at a mean beclomethasone-equivalent dosage of 2142 (range: 500–4000) µg per day. All except two were taking a long-acting β₂-agonist, and 7 were taking a maintenance OCS (mean dosage 25.6 mg/day; range: 4–60 mg/day).

Omalizumab treatment and discontinuation

All patients had started omalizumab between June 2003 and January 2010, and had discontinued it between May 2005 and December 2011. The average duration of treatment was 22.7 ± 13.1 months (median: 22.1 months; range 2.5–59.5 months; Table 2), and the duration of satisfactory on-treatment control of the disease was 15.1 ± 11.8 months (range 0–56.2 months). Before discontinuation, the mean time free of exacerbations was 8.7 ± 7.7 months.

The response to omalizumab was considered 'excellent' (indicating complete response) in 32 patients (52.5%) and 'good' (indicating marked improvement) in the other 29 (47.5%), with particularly good results in the youngest patients 87.5% of 6–11-year-olds had 'excellent' response. In parallel, 45 patients (73.8%) reported improvement in comorbid allergic disorders (including perennial rhinitis, seasonal allergic rhinitis, conjunctivitis and sinusitis).

At the time of discontinuation, physicians were asked to provide asthma control criteria used to justify the decision to discontinue omalizumab treatment: absence of any exacerbation and no need of any OCS were mentioned first; 96.7% and 82% respectively. All physicians had documented at least one asthma control criteria: no exacerbation, no OCS, lung function improvement, daytime and/or nocturnal symptoms improvement, no limitation of activities, no need for rescue treatment, and/or ACT/ACQ. Asthma Control Test was recorded for 22 patients (36.1%). Although most patients (95.1%) were still using ICSs at the time of discontinuation, the mean dosage had decreased by about

Table 1 Demographics and asthma characteristics at the time of the prescription of omalizumab.

Parameter	Study population (n = 61)
Age (mean ± SD) [range]	40.7 ± 20.31 [6–82]
6–11 years, n (%)	8 (13.1)
12–17 years, n (%)	6 (9.8)
≥18 years, n (%)	47 (77.0)
Female, n (%)	40 (65.6)
Bodyweight (mean ± SD) (kg)	69.7 ± 22.8
Height (mean ± SD) (cm)	161.3 ± 15.5
BMI (mean ± SD) (kg/m ²)	26.2 ± 6.7
<i>Asthma characteristics</i>	
Duration of asthma (years)	22.3 ± 15.7 [2–70] 1
Mean ± SD [range] MD	
Total IgE (IU/mL)	544 ± 844 [29–5000] 1
Mean ± SD [range] MD	
<30 IU/mL, n (%)	1 (1.7)
30–700 IU/mL, n (%)	45 (75.0)
≥700 IU/mL, n (%)	14 (23.3)
FEV ₁ (mL)	1962 ± 873 [820–4630]
Mean ± SD [range]	
FEV ₁ (% predicted)	72 ± 24 [27–161]
Mean ± SD [range]	
Daily ICS dosage	2142 ± 997 [500–4000] 6
(µg, BDP equivalent) (n = 54)	
Mean ± SD [range] MD	

BDP, beclomethasone dipropionate; BMI, body mass index; ICS, inhaled corticosteroid; MD, missing data; SD, standard deviation.

13% compared with baseline. Also at discontinuation, no patients were using an OCS (this was an exclusion criterion). 3 patients had discontinued long-acting β₂-agonist therapy (although 91.8% were still taking one). The respiratory function was improved with an average increase of 343 mL (+13% of the predicted value).

Time to loss of control

After discontinuation, the median follow-up time (i.e. either time to loss of control or the period between discontinuation of omalizumab and the last date on which data were available for a patient with sustained control) was 9.3 months (mean: 12.1 ± 9.8 [95% CI: 9.6–14.5]). Loss of asthma control was documented in 34 (55.7%) patients (Table 3): 26 (55.3%) of those who were adults at the time of omalizumab prescription, six (75%) of the 6–11 year-olds and two (33%) of the 12–17 year-olds. Loss of control occurred in 9 (69.2%) of the 13 patients who had received omalizumab for <1 year (median follow-up time: 16.8 months); 13 (59.1%) of the 22 patients who had been treated for 1–2 years (median follow-up time: 10.3 months); and 12 (46.1%) of the 26 patients treated for >2 years (median follow-up time: 7.5 months).

The median time to loss of control after discontinuation was 13.0 months (mean 20.4 ± 2.6 months; 95% CI: 8.3–28.1). The criteria defining loss of control in the 34 patients were: an exacerbation requiring OCS, with control not restored 1 month after the last dose of OCS, in 11 (32.3%); two exacerbations requiring OCS within 1 year in

Table 2 Omalizumab treatment.

Parameter	Study population (n = 61)
Duration of omalizumab treatment (months)	22.7 ± 13.1 [2.5–59.5]
Mean ± SD [range]	
6–11 years (n = 8)	24.3 ± 7.1 [13.0–36.6]
12–17 years (n = 6)	24.7 ± 10.1 [9.2–35.4]
≥18 years (n = 47)	22.2 ± 14.3 [2.5–59.5]
Dosage of omalizumab (mg/month)	426 ± 233 [75–900]
Mean ± SD [range]	
Duration of asthma control before discontinuation (months)	15.1 ± 11.8 [0–56.2] 3
Mean ± SD [range] MD	
6–11 years (n = 8)	17.9 ± 7.9 [8.9–33.54]
12–17 years (n = 6)	17.9 ± 10.6 [0–29.9]
≥18 years (n = 44)	14.1 ± 12.57 [0–56.2]
Time free of exacerbations prior to discontinuation (months)	8.7 ± 7.7 [0.2–30.1]
Mean ± SD [range]	
<i>Global evaluation of treatment effectiveness at discontinuation</i>	
- Excellent	52.5%
- Good	47.5%
Gain in FEV ₁ vs baseline (% predicted)	13 ± 20 [–23 to 72] 8
Mean ± SD [range] MD	
Change in ICS dose vs baseline (µg, BDP equivalent)	–278 ± 494 [–1900 to 600] 2
Mean ± SD [range] MD	

BDP, beclomethasone dipropionate; FEV₁, forced expiratory volume (1 s); ICS, inhaled corticosteroid; MD, missing data; SD, standard deviation.

16 (47.1%); and guideline-based criteria of poor control (at least 3 GINA criteria/increase in ACQ score >1.5/ACT score <19) lasting at least 4 weeks in 11 (32.4%). Some patients met more than one criterion for loss of control.

In the other 27 patients, asthma control was maintained through to the end of their follow-up period. Thus, data are available for all 61 patients at Month 5.4 after discontinuation; by that time, loss of asthma control had occurred in 15. Between Month 5.4 and Month 12, loss of asthma control was documented in a further 11 of the 46 patients still under control at the beginning of that period. In the remaining 35 patients, sustained control was documented from Months 12–23; follow-up ended without loss of control between 5.4 and 12 months in 12 patients. Only 6 patients had >2 years of follow-up, and sustained control was documented in four of these.

Time to loss of control was longer in the 32 patients with an 'excellent' response (median: 17.0 months) compared with the 29 patients with a 'good' response (median: 12.8 months); however, comparison of the survival curves for these sub-groups (data not shown) did not detect any statistically significant effect. Time to loss of control/follow-up censoring as a function of the length of the course of

Table 3 Loss of control and follow-up times.

Loss of control (n = 61)	34 (55.7%)
- <1 year treatment (n = 13)	9 (69.2%)
- 1–2 years' treatment (n = 22)	13 (59.1%)
- >2 years' treatment (n = 26)	12 (46.1%)
Follow-up time (n = 61)	9.3/12.1 ± 9.8
Median/mean ± SD	
- <1 year treatment (n = 13)	16.8/17.8 ± 11.8
- 1–2 years' treatment (n = 22)	10.3/12.5 ± 11.2
- >2 years' treatment (n = 26)	7.5/8.9 ± 5.5
<i>Time to loss of control (months)</i>	
Median/mean ± SE	
-Total population (n = 34)	13.0/20.4 ± 2.6
- 'Excellent' response (n = 17)	17.0/20.8 ± 3.8
- 'Good' response (n = 17)	12.8/12.5 ± 1.4
- <1 year treatment (n = 13)	17.0/22.5 ± 4.7
- 1–2 years' treatment (n = 22)	12.8/11.2 ± 1.5
- >2 years' treatment (n = 26)	9.0/7.1 ± 0.5

SD, standard deviation; SE, standard error.

omalizumab treatment is shown in Fig. 1. No early loss of control (i.e. within 6 months following discontinuation) was observed among patients with >3.5 years continuous omalizumab treatment.

No effect on time to loss of control was detected in a comparison of survival curves stratified on the basis of duration of treatment, or in a univariate analysis of this factor (data not shown). Additionally, no relationship was detected between time to loss of control and either the dosage administered or the duration of satisfactory control before the discontinuation of omalizumab.

Resumption of omalizumab

Of the 34 patients in whom asthma control was lost, 20 (58.8%) were re-prescribed omalizumab. Response to omalizumab re-treatment was considered 'excellent' in 6 patients (30%) and 'good' in 8 patients (40%). Of the remaining 6 patients, 4 (20%) did not respond to re-treatment, and two

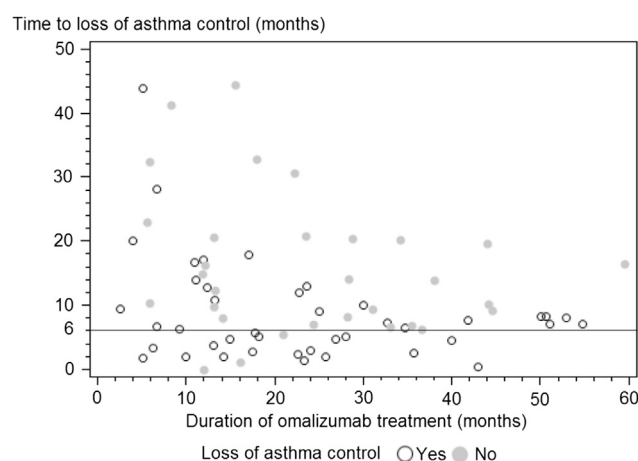


Figure 1 Time to loss of control/follow-up censoring as a function of the length of the course of omalizumab treatment.

could not be assessed for response because the duration of follow-up was too short.

Discussion

This retrospective, observational study suggests that discontinuing omalizumab after control has been obtained in patients with severe, persistent, allergic asthma is without any rebound effect. Asthma control was lost in 34 patients (55.7%) after a median period of 13 months following the discontinuation of omalizumab. However, none of the patients with loss of asthma control within 6 months of stopping treatment had been treated with omalizumab for >3.5 years. This would suggest that the risk of early loss of control is small after a long enough course of treatment.

The average duration of omalizumab treatment prior to discontinuation was nearly 2 years, but the range was wide, from just 10 weeks to nearly 5 years. Similarly, very different criteria were used by different physicians to define satisfactory control on treatment, and there was wide variability in the duration of omalizumab treatment once asthma was controlled on treatment, from zero (i.e. treatment was stopped as soon as control was established) to >4.5 years. These observations illustrate the divergence in clinical practice among respiratory specialists. This might be expected with a relatively new drug for which the prescribing information is succinct, especially concerning discontinuation criteria. In the present study, patients in whom the response to omalizumab treatment had been judged as excellent remained controlled, post-discontinuation, for longer than those in whom response was judged as good (median 17 versus 13 months, respectively). This might indicate that degree of response while still on treatment is a useful indicator of persistency of effect, although no statistically significant relationship was detected between time to loss of control and either response on treatment, or duration of satisfactory control before discontinuation of omalizumab.

As well as the degree of response and its duration, many other factors should be taken into account when deciding whether to stop omalizumab treatment, including: the history of the severity of the disease; the need for other drugs, together with their relative advantages and disadvantages (notably OCS); adverse reactions; pregnancy; environmental changes (e.g. the risk of parasitic infections); comorbidities (notably, the impact of other allergic manifestations on quality of life, and the effectiveness of omalizumab against them); and patient preferences.

In more than 75% of patients who were re-treated with omalizumab after asthma control was lost, responses to re-treatment were judged as 'excellent' or 'good', and four out of 20 patients did not respond to omalizumab re-treatment. However, in the absence of a control arm in which patients did not discontinue omalizumab, we cannot exclude the possibility that some patients could have experienced deterioration of their condition despite continued treatment.

This real-life study has limitations. In particular, because omalizumab has only been available in France since 2006 for adults and adolescents and 2009 for children, patients who received a longer course of treatment tended to have a shorter follow-up. Our results suggest that loss of

asthma control following omalizumab discontinuation is more likely in patients treated for a shorter length of time (Table 3). However, the results are difficult to interpret, because patients with shorter durations of treatment also had longer follow-up times. It is possible that differences in loss of asthma control would have been less pronounced, or would have disappeared altogether, if the follow up times had been the same for each of the treatment duration subgroups. It is important to note that no delayed loss of control (i.e. occurring >30 months after the discontinuation of omalizumab) was observed in patients treated for more than two years. However, this could be because the follow-up period was too short. This study does not allow any definitive answer on the optimum duration of omalizumab treatment. However, the results suggest that the risk of early loss of control is small after a long enough course of treatment.

Given the frequent reluctance of patients to embark on any lifelong treatment, it is important for prescribing physicians to be able to offer hope that discontinuation might be possible under certain conditions. To date, there have been no data from appropriately designed clinical trials that would inform when to discontinue treatment.

Data from follow-up of the INNOVATE clinical study showed that IgE levels climbed back up to pre-treatment levels after the end of a 6-month course of treatment and that this correlated with symptom score, back-up drug consumption and impaired lung function [14]. However, after discontinuation at the end of a 6-year course of omalizumab, the beneficial effects of the treatment were sustained through three years in 12 out of 18 members of a cohort of cat-allergic Swedish patients [15], a long-term effect which the authors ascribed to permanent desensitisation of basophils, i.e. the interruption of a vicious cycle.

So, targeted clinical trials need to be performed to establish evidence-based discontinuation criteria, notably to define the optimum duration of treatment (especially in the light of preliminary results suggesting that a sufficiently long course of omalizumab may have a disease-modifying effect [16]) and identify reliable predictors of sustained control after discontinuation.

This could be remedied by the XPORT study (NCT01125748), which is currently underway in the United States, which investigates the impact of omalizumab withdrawal on clinical outcomes over a 1-year period, following successful 5 years of therapy. Results are expected during 2014. It may take some years to accumulate sufficient data on outcomes in patients who have discontinued omalizumab after extended courses of treatment, especially under real-life prescription conditions. It inevitably takes time to accumulate long-term data on a recently licensed drug, but severe, treatment-refractory asthma is a major public health problem, and efforts to collect such data are warranted.

In conclusion, these data offer insights into the discontinuation of successful omalizumab treatment in severe asthmatic patients. In this real world setting, asthma control was maintained in about half of patients following treatment discontinuation, particularly for the patients who were on longer duration treatment. Discontinuation was not associated with any rebound effect. Further studies are needed to better define the criteria for omalizumab

discontinuation, as this may help to reduce the risk of subsequent loss of asthma control.

Conflict of interest statements

Prof Molimard is a consultant and participated at advisory board meetings organised by Novartis Pharma SAS; Bristol-Myers Squibb Company; GlaxoSmithKline plc; Merck Serono SA; Pfizer, Inc; and Stallergenes S.A. Laurence Mala, Isabelle Bourdeix, and Vincent Le Gros are employees of Novartis Pharma.

Acknowledgements

The authors thank the staff at the participating clinical centers. The study was funded by Novartis Pharma, Rueil-Malmaison, France. The authors were assisted in the preparation of manuscript by Felicity Neilson from Matrix (Paris, France) and Richard Crampton (Novartis).

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