

A STEP-DOWN PROTOCOL FOR OMALIZUMAB TREATMENT IN ORAL CORTICOSTEROID-DEPENDENT ALLERGIC ASTHMA PATIENTS

Running title: Omalizumab dose-decreasing protocol.

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Abstract.

Background: there are no specific criteria for a step-down or withdrawal dose of omalizumab. Our purpose was to evaluate the viability of a protocol for **OMAlizumab DOse REduction** (the OMADORE study) in severe allergic asthma (SAA).

Methods: the study population included 35 SAA patients treated during a minimum period of one year with oral corticosteroids (OC) equivalent to a mean daily dose of 4 mg of methylprednisolone. To qualify for the protocol, the patients had to have received treatment with OMA $\geq$ one year and a half, OC dose had to have reached the lowest tolerated dose and spirometry had to be $\geq$ at entry. Intervention: a) OMA dose was reduced by half; b) if patients were clinically stable after 6 months, the dose was halved again; c) if repeated OC boosters were needed and/or spirometry worsened $\geq 10\%$, OMA dose was raised to the previous figure until stabilization.

Results: Mean age was 52.5 (17) years, median monthly OC dose was 120 (IQR: 225) mg. Pulmonary function: FVC: 79.7 (20.2)%; FEV₁: 64.8 (21.7)%; FEV₁/ FVC: 61.7(13.8)%. OMA could be withdrawn in 34.3% of the patients; 22.9% tolerated a reduction, and in 42.9% the dose could not be modified. Follow-up time after reduction or withdrawal ranged from 12 to 30 months. There were no severe exacerbations requiring emergency assistance or admission.

Conclusions: The OMADORE study found that in more than 50% of SAA patients on OC, OMA dose can be safely reduced or withdrawn based on a progressive dose reduction protocol.

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Key words: severe allergic asthma; omalizumab; treatment step-down; omalizumab withdrawal.

What is known about this subject

There are no recommendations for omalizumab withdrawal. Our study is the first report in the literature of a step-down protocol for severe asthma patients treated with omalizumab.

What this study adds

In around a third of allergic oral corticosteroid-dependent asthma patients, omalizumab can be safely withdrawn between two and four years after initiation of treatment.

Tables of Links

TARGETS
Immune checkpoint proteins
Immunoglobulins

LIGANDS
Omalizumab

These Tables list key protein targets and ligands in this article that are hyperlinked to corresponding entries in <http://www.guidetopharmacology.org>, the common portal for data from the IUPHAR/BPS Guide to PHARMACOLOGY [1], and are permanently archived in the Concise Guide to PHARMACOLOGY 2015/16 [2].

Introduction

The last update of the Global Initiative for Asthma (GINA) stresses the importance of controller medication. Omalizumab (OMA) (Xolair Novartis®), a murine immunoglobulin E (IgE) monoclonal antibody (mAb) blocking agent marketed since late 2006 (3), is currently recommended for unstable allergic GINA step IV and GINA step V asthma patients, before the administration of oral corticosteroids (OC) (4). Encouraging results with off-label prescriptions of OMA (5-8) have also been reported. OMA initially showed a sparing effect of inhaled corticoids (4), and two recent studies have also shown its oral corticosteroid-sparing effect in severe allergic asthma patients (9, 10).

Omalizumab reduces free serum IgE by 99% within two hours; downregulates IgE receptors on basophils, mast cells and dendritic cells after three months; reduces the number of eosinophils in sputum and bronchial biopsies; reduces exhaled nitric oxide, and downregulates IgE production. Since patients may take a considerable time to stabilize, at present it is not clear how long OMA treatment should be maintained – or, in other words, when physicians can begin to consider its withdrawal.

The evidence from some of the studies discussed below indicates that at least some patients seem to tolerate OMA withdrawal. However, the evidence is weak and the percentages, and the patient's phenotype, are unknown. The purpose of the **OMAlizumab DOse REDuction**

(OMADORE) study is to describe our experience in a cohort of patients treated with OMA in whom a dose-decreasing protocol was implemented at our service.

Material and methods.

The hypothesis to be tested was whether, after a relatively long period of treatment, OMA dose could be safely reduced or withdrawn in a subset of patients, without diminishing its oral corticosteroid-sparing effect or its ability to control asthma.

Population: Patients were recruited from the outpatient clinic for asthma treatment at our institution (3). The inclusion criteria were: 1) Age ≥ 18 years old; 2) Obstructive airway disease with a forced expiratory volume in the first second (FEV₁) reversibility $\geq 12\%$ and 200 mL; 3) Steroid-dependence: defined either as a requirement of a mean daily dose of at least 4 mg per day of methyl-prednisolone to maintain an FEV₁ $\geq 50\%$ during a period of one year or more in addition to the best standard care provided by GINA (1), or as repeated boosters equivalent to a mean daily dose of 4 mg of methyl-prednisolone during the previous year; 4) Positive skin-prick test or in vitro reactivity (ImmuneCAP); 5) Baseline immunoglobulin E level ranking between 30-700 IU/mL; 6) Patient weight between 25 and 150 kg; 7) When starting the OMA dose reduction, the oral corticosteroid dose had to have reached its lowest level (ideally zero) and spirometry had to be $\geq$ at entry; 8) Patients had to have received treatment with OMA for $\geq$ one year and a half.

The exclusion criteria were: 1) Patient's refusal of treatment; 2) Hypersensitivity to OMA; 3) Inability to regularly attend the asthma unit for control and drug administration.

Study design: Single-center, open-label intervention study.

Setting: The study was performed at the Corporació Sanitària Parc Taulí (CSPT), a 760-bed university hospital in Sabadell, Catalonia, between July 2006 and July 2014.

Treatment protocol: Best standard care following the GINA recommendations, as described elsewhere (6). Prior to starting OMA treatment, patients underwent a stabilization period of at least three months. The protocol followed for decreasing OC was also described elsewhere (7,9). The dose of OMA was calculated according to the dosing tables previously published by the European Medical Agency (4).

Step down protocol: To qualify for the protocol, the patients had to have received treatment with OMA $\geq$ one year and a half, OC dose had to have reached the lowest tolerated dose and the pulmonary function tests (PFTs) had to be $\geq$ at entry. All patients included were

considered responders according to GETE (global evaluation of treatment effectiveness) between weeks 16-24. (figure 1).

Intervention: a) The OMA dose was reduced by half; b) if clinically stable for six months, the dose was halved again; c) if needed, OC boosters were administered; d) when more than one OC booster was needed and/or PFTs worsened, OMA dose was raised to the previous figure until the patient stabilized (figure 1). Patients were visited every four weeks (to facilitate reporting, we consider one month = 4 weeks). At each visit a forced spirometry and FeNO measurement were performed; e) at each outpatient visit, patients were asked to describe their asthma treatment and their total monthly OC intake was recorded. In the case of exacerbation, patients were asked to come to the hospital, if possible to the outpatient center at our pulmonary service during business hours rather than the emergency room (ER) in order to facilitate treatment control. Nonetheless, as the clinical histories at the hospital are computerized, data on patients who came to the ER were also recovered (as well as data on their discharge treatment).

Patients were classified into three groups according to their clinical response: 1) Intolerant: patients who never met the criteria for applying the step-down dose, plus those who failed the first attempt at dose reduction; 2) Partially tolerant: patients who tolerated reduction or withdrawal, but who needed reintroduction of the drug at a dose lower than the initial one; 3) Tolerant: patients who tolerated drug withdrawal. When OMA was withdrawn or reduced, or if patients were considered intolerant to dose reduction, spirometry, FeNO and medical visit were performed every three months.

Outcomes: The primary outcome was to establish the percentage of patients who would tolerate a step down protocol (OMA withdrawal or a dose decrease) without severe exacerbations. The primary safety outcomes were to estimate monthly OC intake, lung function (FEV₁) and airway inflammation (exhaled nitric oxide). The second safety outcome was to detect the treatment's side-effects.

Definition of severe exacerbation: exacerbation requiring a burst of OC or doubling of the baseline dose of OC >3 days each, plus an unscheduled visit to the hospital or the emergency room or hospital admission. Since all patients were taking OC and were trained to increase or decrease the dose depending on their necessities, an increase (or booster) in the OC dose by itself was not used as a criterion to define severe exacerbations.

Instrumentation and side effect monitoring: During the protocol period, forced spirometry, prick test, FeNO measurement, blood analysis (including hemogram, IgE concentration and specific IgE (ImmuneCAP) and imaging tests were performed as previously described (7).

Spirometry and FeNO were measured at each monthly visit. Once the protocol period was considered ended (that is, when OMA was withdrawn or patients did not tolerate OC and/or OMA reduction) patients were considered stabilized and visits were adapted to their necessities (usually every three months). Then, from this point onward, no systematic spirometry or FeNO measurements were obtained. These data are not given.

Patients were specifically asked about side effects at each visit. They were also given the telephone number of the outpatient unit of the pulmonary service and told to report any suspected side effects.

Statistical analysis: Descriptive statistics include frequencies and percentages for categorical variables and means and standard deviations for continuous variables. A parametric test (Student's t test for paired data) was used to compare the initial and end corticosteroid dose, FeNO and spirometry. ANOVA was used to compare the monthly dose of OC intake. A p-value < 0.05 was considered statistically significant. The analysis is presented for the full cohort plus the three subgroups (intolerant, partially tolerant and tolerant).

The study was approved by the Ethics committee of the Hospital (CEIC/CEIm Institut d'Investigació i Innovació Parc Taulí; FIS código CDR-OMA-2012-01/PI11/02303) and informed consent was obtained from all patients.

Results

Forty-three patients were included. Eight of them did not follow the protocol, for a variety of reasons. The flow chart is given in figure 2. The remaining 35 patients were analyzed (table 1). Twelve patients tolerated the dose decreasing protocol (34.3%) until drug withdrawal. Among the remaining 23 patients, twelve did not fulfill the criteria for the dose decreasing protocol and three more did not tolerate a first attempt; thus, the protocol could not be implemented in 15 out of 35 (42.9%) patients. Of the remaining eight patients, five tolerated a dose reduction but not a withdrawal and three tolerated a temporary withdrawal but needed to reinstate the treatment; thus, the total number of patients tolerating a dose reduction but not withdrawal was 22.9%.

There were no differences in age (mean age of the whole group: 51.7 ± 17 years; tolerant group 44.1 ± 4.2 ; intolerant + partially tolerant: 55.7 ± 3.7 ; p-value between these two subgroups 0.057) or sex distribution. Figure 3 shows the time-sequence withdrawal of OMA. Note that in all cases the protocol lasted for between 18-40 months. After this intervention period, there were no more withdrawals.

The dose reduction and withdrawal in tolerant and partially tolerant groups respectively are given in tables E1 and E2. The full data were analyzed at month 48. Patients were followed during an additional period that ranged between 12-36 months, depending on the patient.

Severe exacerbations: there were no severe exacerbations.

Oral corticosteroid decrease: Figures 4-A and B show the reduction in consumption of OC in the tolerant group, which reached zero in all cases by the end of the follow-up. In the partially tolerant group, OC consumption showed a downward trend, despite the reduction in OMA dose. In the intolerant group, corticosteroid intake was erratic from the beginning and there were no relevant changes in overall OC consumption.

Forced spirometry tests (figure 5). Overall, the tolerant group showed a progressive improvement in spirometry, with a mean FEV₁ increase already in the first month of 0.37 ± 0.73 mL ($10.9 \pm 21.4\%$). The spirometry values were higher throughout the follow-up than in the other two groups, despite OC and OMA withdrawal. The intolerant group always had the worst spirometry results. At the end of the 48-month period, the FEV₁ of the partially tolerant group was very similar to that of the intolerant group.

Th2 response markers (figure 6). Figures 6-A and 6-B show a trend in the tolerant group toward a greater reduction in eosinophils at month 6 and at the end of follow-up than in the other two groups, though these differences did not reach statistical significance. No differences in FeNO values were observed between groups. IgE values increased in all groups in response to the blocking effect of OMA. The end measurement represents the date OMA was withdrawn, and is therefore not uniform for the whole cohort.

Omalizumab dose reduction: Analyzing the three groups together, the protocol achieved an overall mean reduction of OMA consumption of 44.2%.

Predictors of response to protocol: Several predictive models of response to the protocol were analyzed with the variables included in the study. It was not possible to define a definite predictive phenotype. However, the following conditions – improvement of FEV₁ of 100mL in the first month plus a 50% reduction in OC consumption in the sixth month without an increase in eosinophil counts and FENO values <50 ppb – occurred in five out of 12 (41.6%) of the patients in the tolerant group but in only one out of 15 (6.6%) in the intolerant group.

Side-effects: no relevant side effects were reported by the patients or observed by the research team.

Discussion

OMADORE, an empiric open-label intervention study, is the first prospective analysis specifically designed to determine whether a reduction or withdrawal of OMA dosage is possible. In many other diseases treated with biological agents, the drugs administered can never be discontinued. In patients with severe asthma, physicians have asked themselves whether OMA can be withdrawn, or its dose reduced, in case of clinical improvement. So the aim of the OMADORE study was to establish whether severe asthma would mimic these other immunological conditions or whether, on the contrary, the particularities of the respiratory system (the only system in the body in continuous contact with the atmosphere) would play a major role.

The cohort in the OMADORE study included the most severe patients (GINA step V). We designed and applied a prospective empirical protocol with a rationale based on patient safety. The main overall aim was to avoid severe exacerbations attributable to the protocol and caused by erroneous clinical decisions. After starting OMA treatment, we progressively reduced the OC dose as far as the patient was able to tolerate. It should be noted that some patients never met the criteria for implementation of the protocol, while others who were included continued to require a minimum OC dose. No severe exacerbations related to the protocol were observed, nor any relevant side effects. As expected, the clinical benefits of OMA treatment were evident in all patients despite the decrease in OC consumption. The overall OMA saving was slightly below 50%. Thirty-four per cent of patients tolerated OMA withdrawal, 23% tolerated a decrease in the dose and 43% did not tolerate the decrease. The saving was obtained without any relevant exacerbations.

To date, several unsuccessful attempts have been made to address the issue of OMA reduction or withdrawal. Discontinuation of OMA in atopic subjects has led to a new increase in serum IgE and its FcεRIα receptors (11), immediate allergen skin test reactivity (12) and asthma symptoms (13). In 2011, Lowe and Renard (14) published a model suggesting the possibility that OMA can be safely withdrawn after a 5-year treatment period. This results were consistent with those of Nopp et al (15,16). However, these findings were discordant with some other clinical studies (17, 18).

In the XPORT study (19), 175 patients receiving OMA for ≥ 5 years were randomized either to continue the same dose of OMA or to switch to placebo, and were followed for one year. The OMA group showed a higher proportion of exacerbation prevention (19.3%, representing a 40% relative difference between groups), better symptom control, and a longer time to first protocol-defined exacerbation. The study had the following limitations: it did not establish

the time to treatment discontinuation, since it included patients in whom the treatment period was uncontrolled (though it was always longer than five years); it assumed that the treatment should be withdrawn abruptly; it mixed moderate and severe patients; and finally the length of follow-up after withdrawal was too short. The clinical interpretation is that long-term treatment maintenance offers better clinical outcomes, but that there seems to be a percentage of the population who can safely tolerate treatment withdrawal. Taken together, the studies published to date have not addressed the questions raised by OMADORE.

The OMADORE study considered patients as responders according to the GETE criteria. Those who were mild responders after four months were evaluated again after six months. When it was decided to continue OMA treatment, the OC dose was progressively reduced. In a previous study in severe asthma patients treated with methotrexate (5), we observed that some patients started to respond after 9-10 months of treatment (20). As a result, we decided to maintain the treatment with OMA for at least 12 months after classifying the patient as a responder, which gave a minimum period of 18 months before considering whether to decrease the OMA dose. This does not mean that a dose reduction was systematically applied at month 18. As noted above, according to the Lowe and Renard (14) model, the production of IgE falls notably after some years of treatment, but the exact period is not well established. Although the concentration of free IgE may increase and thus introduce an element of risk in the protocol it should be borne in mind that the receptors for IgE are internalized after several months of treatment with an anti-IgE; therefore, we did not consider that a progressive decrease of OMA dose after a minimum of 18 months of treatment would represent a risk for the patient.

According to the protocol, the time to withdrawal is related to, or depends on, the patient's initial OMA dose; it is longer in patients receiving higher OMA doses. Therefore, we were unable to establish a fixed date for OMA withdrawal.

Regarding the Th₂ marker response, we observed that blood eosinophils had fallen in all groups at the end of the follow-up, but more markedly in the tolerant group. FeNO values did not help to distinguish between groups; in the tolerant group, however, the values did not increase despite OMA and OC withdrawal.

The interpretation of the IgE values may be confusing. Total IgE concentration increased 2-3 fold (9) after OMA treatment because trimers and examers are created between IgE and the OMA molecules; they remain in the blood stream longer than non-blocked IgE, since they are cleared more slowly due to the size of the new molecules. For this reason, total IgE has never been considered an adequate parameter for decisions regarding patient follow-up or

treatment. As for free IgE, it is assumed that a 99% reduction in free IgE is needed to achieve clinical response, something that occurs around 4-6 months after the beginning of the treatment (21); but of course some patients are non-responders, and this is why free IgE has not been used as a clinically useful biomarker either.

The IgE values compared in the intolerant and the partially tolerant groups were obtained at month 48, while the values in the tolerant group were obtained when OMA was withdrawn. In the first two groups, the IgE concentration remained high while in the tolerant group it showed a downward trend; in any case, its concentration was lower than at six months. This may reflect a trend toward a decrease in IgE production, perhaps in agreement with Lowe's model (14).

The spirometry showed a trend towards improvement in the tolerant group despite OC and OMA withdrawal. This result has not been reported in the majority of cohorts. No such improvement was seen in the other two groups, whose behavior was quite similar,

Patients with rapid increases in FEV₁ after the first dose of OMA plus a 50% reduction in OC consumption in the sixth month, without any increase in eosinophil count and FENO values <50 ppb, seem to be the ones that tolerate drug withdrawal best. Younger patients also seemed to tolerate the dose reduction better. Overall, this may reflect the fact that, in some patients at least, OMA is a disease-modifying drug, or that it is the less severe patients who tolerate OMA withdrawal best. In any case, tolerance of OMA withdrawal can only be established after a dose reduction trial. The fact is that there are some patients in whom OMA can be safely withdrawn. With the information available it is not clear that the patients who tolerate OMA withdrawal comprise a specific phenotype.

OMA was withdrawn between months 18 and 40. This probably means that in cases in which it cannot be withdrawn before 3.5-4 years, any attempts to do so will be in vain. After withdrawal, patients were followed in accordance with our unit's protocol for severe asthma patients, and we can be sure that there were no severe exacerbations between month 48 and the end of follow-up. Therefore, the conclusion is that around one third of the patients will tolerate OMA withdrawal safely and that this benefit is long-lasting; however, this does not rule out the possibility that some patients will need to re-start OMA treatment in the future.

The limitations of the OMADORE study are related to the protocol design itself. The main overall purpose was to establish whether OMA withdrawal can be safely attempted in some patients, and to determine the period during which it can be withdrawn – something that has not been defined in the literature. Therefore, we did not consider it essential to introduce a placebo arm. We did not aim to evaluate the potential "placebo or nocebo" effect, but rather

to establish a policy to be followed by clinicians in daily clinical practice, similar to the ones proposed by the guidelines for dose reductions in inhaled drugs. The number of patients is relatively low, but it should be borne in mind that OMADORE started shortly after the marketing of OMA and the follow-up period has been very long. This obviously limits the number of eligible patients for evaluation, since the ones treated more recently (and thus with a shorter follow-up) could not be included.

As a conclusion, the OMADORE study has shown that OMA can be safely withdrawn in more than one third of GINA step V asthma patients receiving OC. A progressive decrease seems to be advisable in order to avoid severe exacerbations. In patients in whom OMA can be withdrawn, it seems that treatment can be discontinued between year 2 and 4 after OMA initiation.

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Author's role:

Christian Domingo and Xavier Pomares: design of the study, patient recruitment, treatment and follow-up, writing of the manuscript. Both authors are guarantors of the paper.

Albert Navarro : statistical analysis

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Concepción Montón and Ana Sogo: patient treatment and follow-up

Rosa Maria Mirapeix: statistical analysis and manuscript supervision.

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Table 1. Demographic data.

	All (n=35)		Intolerant (n=15)		Partially tolerant (n=8)		Tolerant (n=12)	
	<i>n</i>	<i>%</i>	<i>n</i>	<i>%</i>	<i>n</i>	<i>%</i>	<i>n</i>	<i>%</i>
Female	24	68,6	11	73,3	5	62,5	8	66,7
	<i>Median</i>	<i>IQR</i>	<i>Median</i>	<i>IQR</i>	<i>Median</i>	<i>IQR</i>	<i>Median</i>	<i>IQR</i>
Omalizumab dose (mg)	300	300	300	150	525	375	300	225
Corticoids (mg)	120	224	300	150	60	202	116	232
IgE (IU/mL)	170	249	132	113,1	370	264,5	150	143,3
FeNO (ppb)	15	31	12	26	13	28	25,5	24,5
	<i>Mean</i>	<i>SD</i>	<i>Mean</i>	<i>SD</i>	<i>Mean</i>	<i>SD</i>	<i>Mean</i>	<i>SD</i>
Body Mass Index (Kg/m ²)	27,4	5,4	28,0	4,0	30,3	7,6	24,7	4,2
EoS (x10 ⁶ /L)	410,6	304,7	350,0	242,0	333,8	255,3	537,5	379,5
EoS (%)	5,1	3,4	4,6	3,0	4,2	2,3	6,2	4,2
FVC (L)	2,8	0,8	2,8	1,0	2,6	0,5	2,9	0,7
FVC%	79,7	20,2	81,6	20,8	77,1	21,8	78,9	20,0
FEV ₁ (L)	1,7	0,6	1,6	0,6	1,8	0,6	1,8	0,5
FEV ₁ %	64,8	21,7	61,5	20,0	71,7	24,0	64,3	23,1
FEV ₁ /FVC%	61,7	13,8	56,4	11,5	69,3	11,6	63,2	15,8

No statistically significant differences were found between groups and variables.

Corticoids: cumulative monthly oral corticoid dose. EoS: blood eosinophil count.

FVC: forced vital capacity. FEV₁: forced expiratory volume in one second.

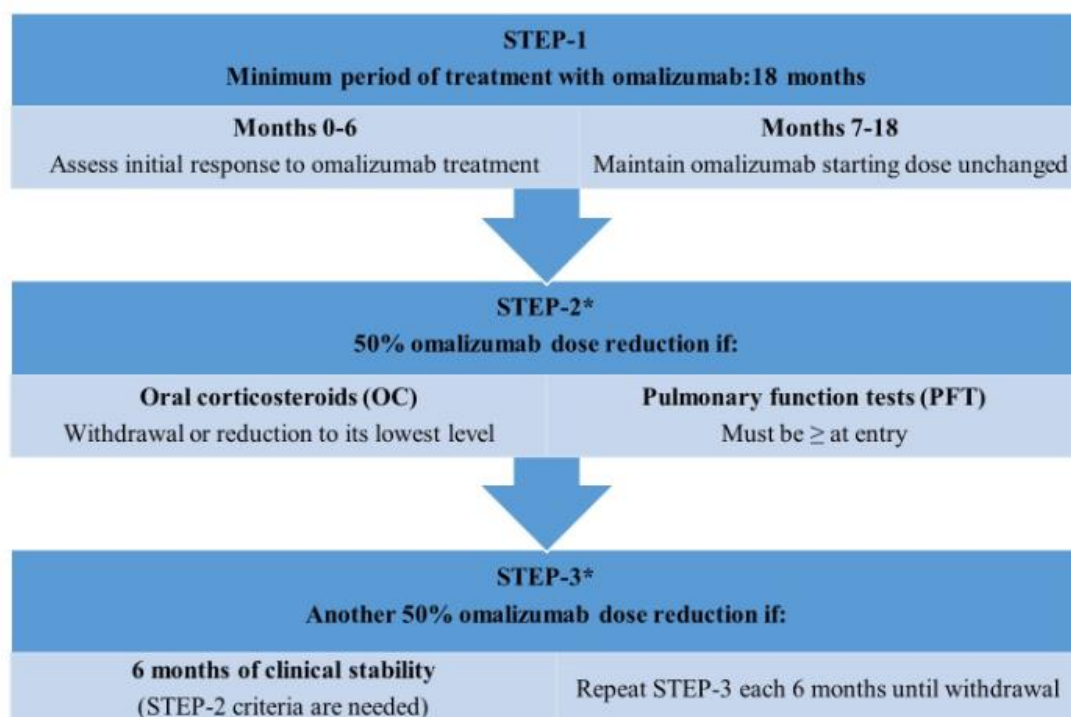


Figure Legends:

Figure 1. OMA dose reduction protocol.

*In the case of loss of asthma control (need for OC boosters and/or PFT worsening $\geq 10\%$) return to the previous STEP.

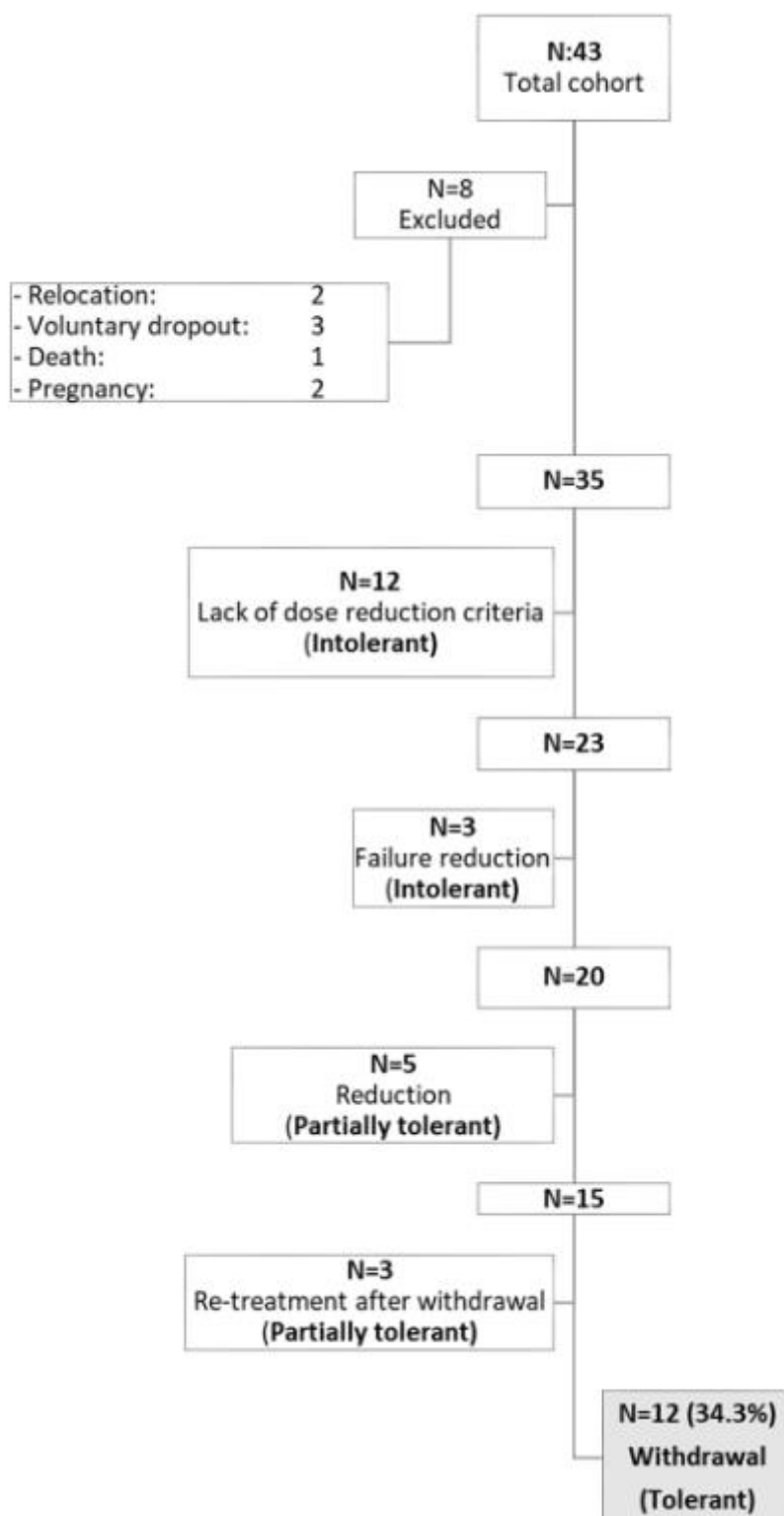


Figure 2. Flowchart.

Number of patients considered tolerant: $12/35 = 34.3\%$; partially tolerant: $5+3/35 = 22.9\%$; intolerant: $12+3/35 = 42.9\%$.

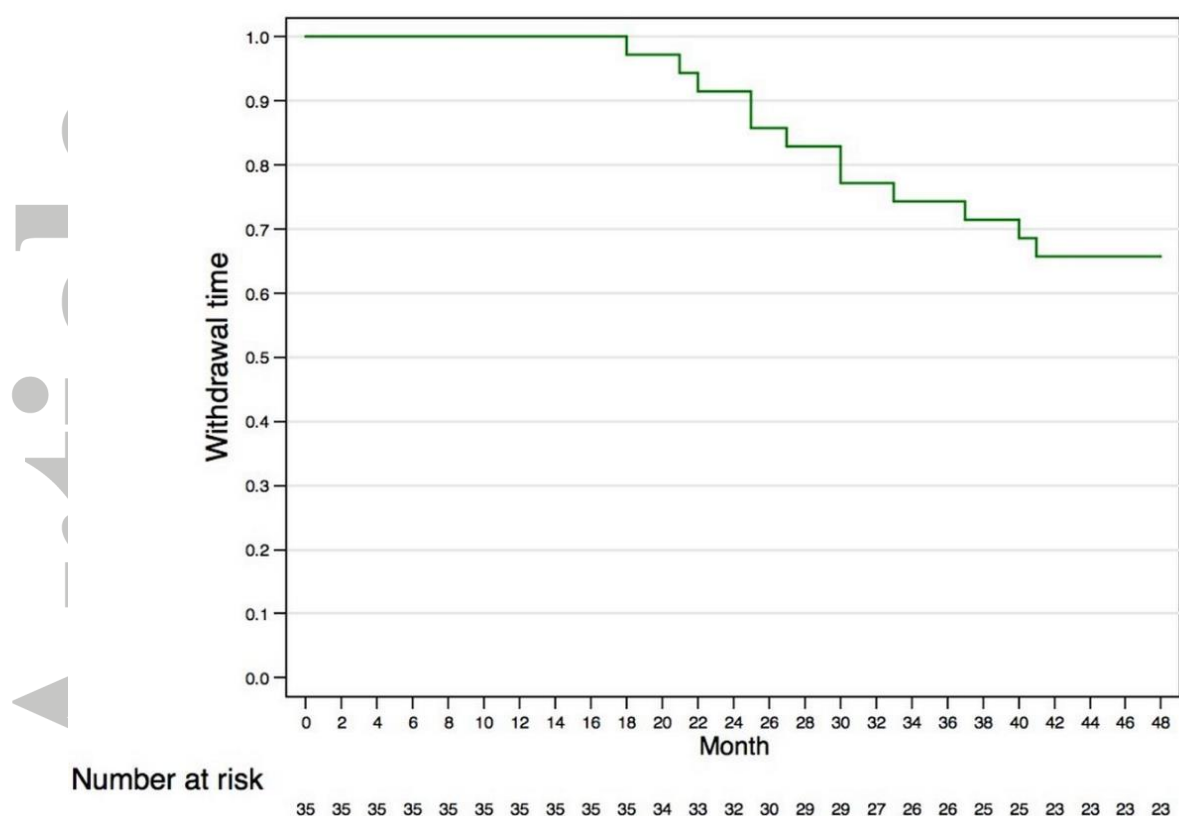


Figure 3. Time-sequence withdrawal of OMA according to the protocol.

The x-axis shows the number of patients treated with OMA at that stage. Note that the first withdrawal occurred at month 18, and thus appears on the x-axis in the following month.

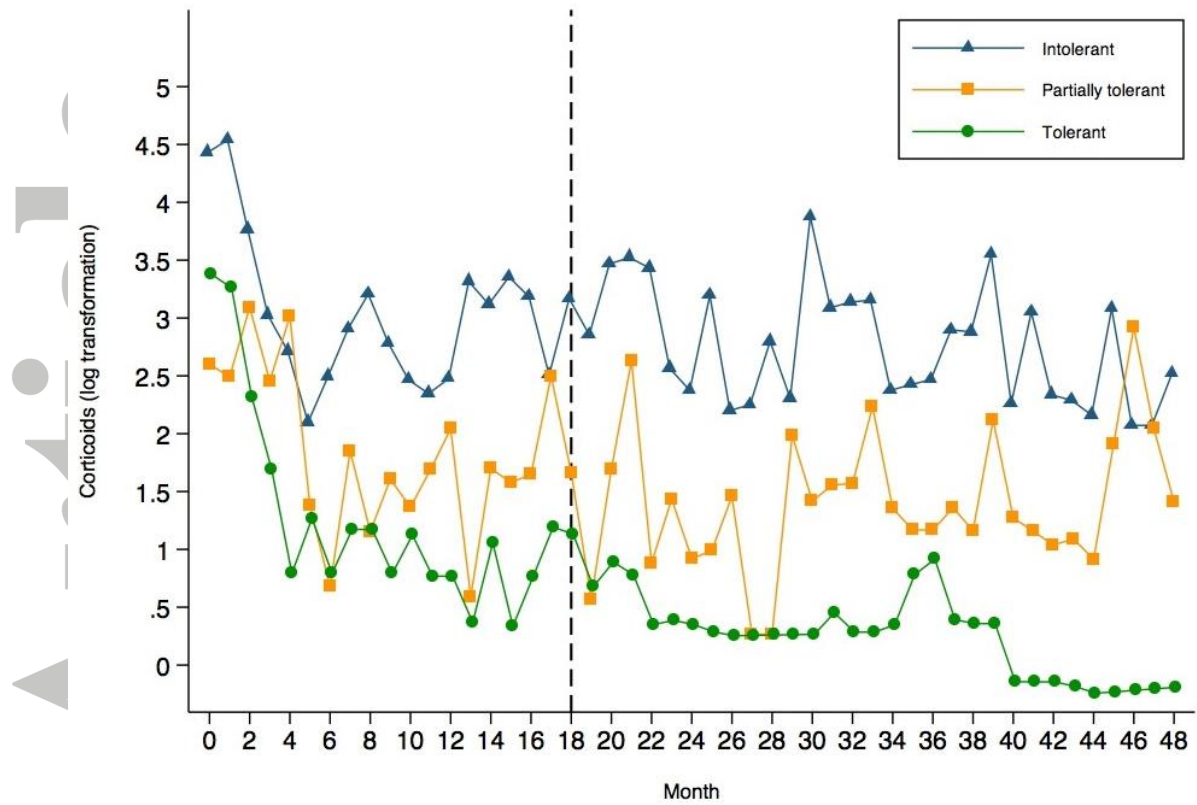


Figure 4. Corticosteroid consumption according to protocol and group

Figure 4-A: shows the mean OC consumption for every group

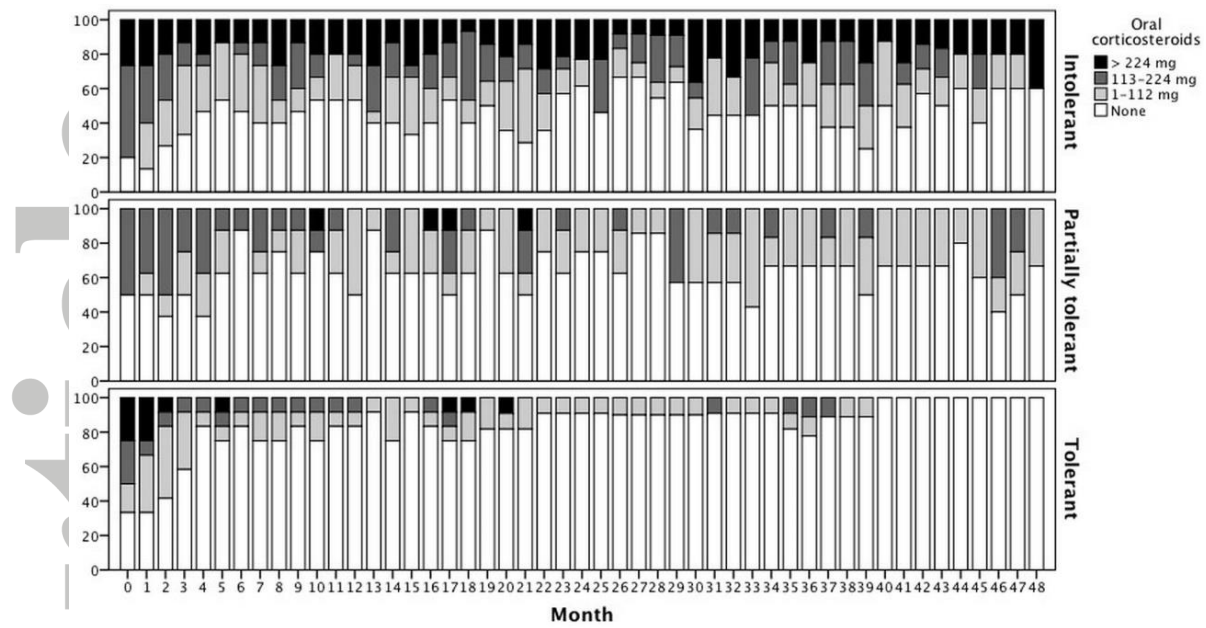


Figure 4-B: shows the different ranges of cumulative OC dose of every group

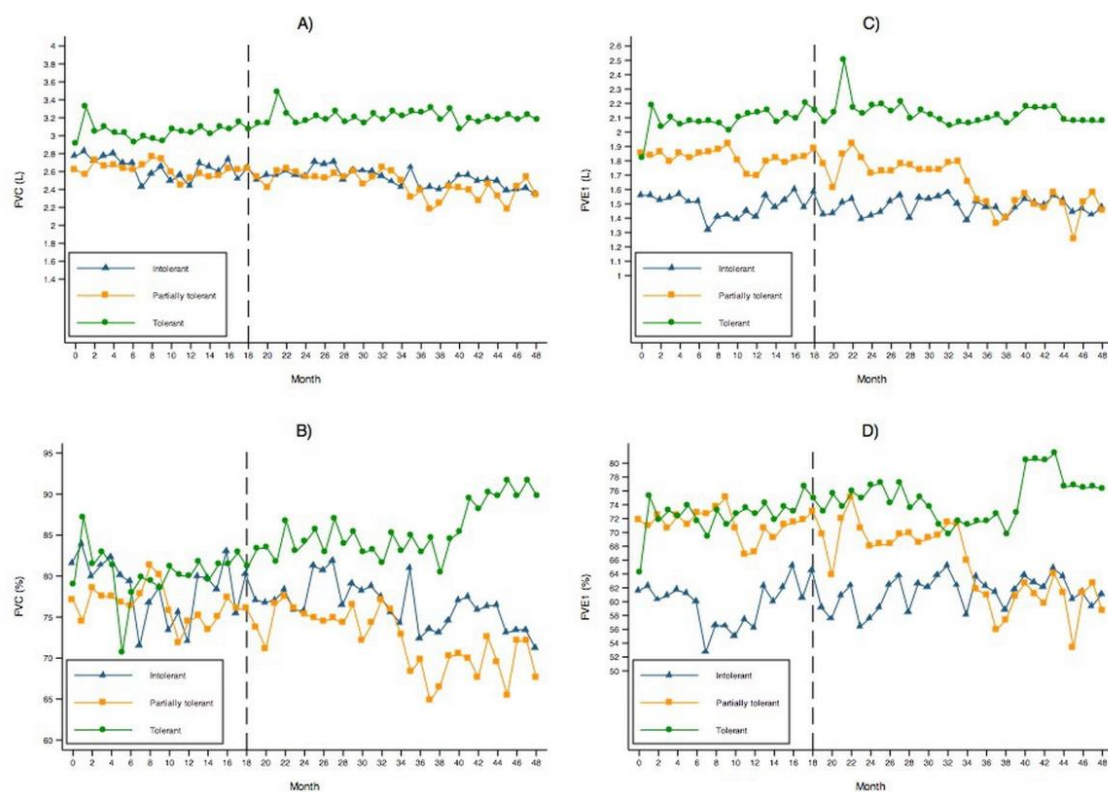


Figure 5. Forced spirometry evolution.

Figures A and B show the FVC values in liters and percentages. Figures C and D show the FEV₁ values in liters and percentages.

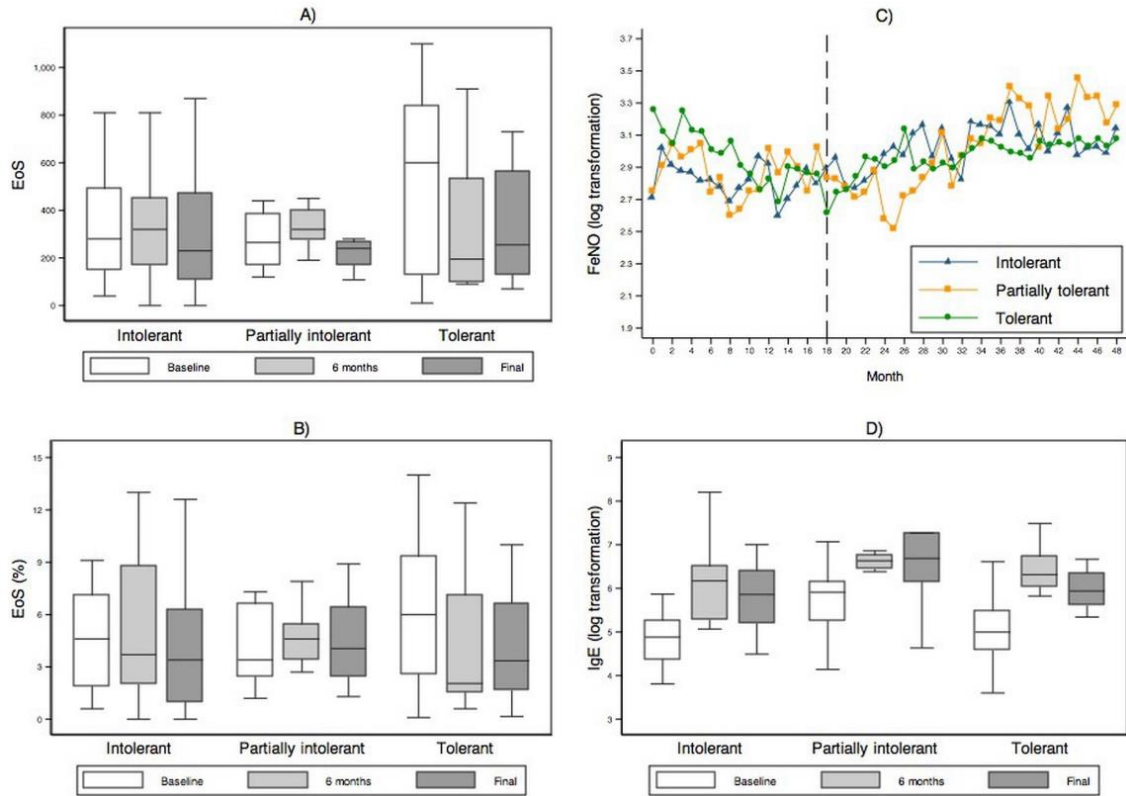


Figure 6. Th2 response markers at entry, month 6 and end.

A and B show the eosinophil values, C the FeNO values and D the IgE concentrations. Eos: eosinophils (overall count and in percentage); FeNO: fraction exhaled of nitric oxide (parts per billion); IgE: immunoglobulin E.

The end measurement represents the date OMA was withdrawn and is therefore not uniform for the whole cohort.

**A STEP-DOWN PROTOCOL FOR OMALIZUMAB TREATMENT IN ORAL
CORTICOSTEROID-DEPENDENT ALLERGIC ASTHMA PATIENTS**

Running title: Omalizumab decreasing protocol

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E-tables 1 and 2

E-Table 1. Cohort of tolerant patients (n=12).

Initial dose of OMA	Time to withdrawal	Follow-up Period
150	18	30
300	42	30
450	36	30
300	24	30
150	18	30
300	24	36
300	36	18
300	30	24
600	30	18
150	30	18
150	30	12
900	48	18

Time is given in months, and dose in mg. The follow-up period refers to the length of time patients were followed after OMA withdrawal. Dose reduction in this subgroup was 100%.

E- Table 2. Cohort of partially tolerant patients (n=8).

Initial dose of OMA	Time to dose reduction	Lowest dose tolerated	Period with lower dose¹	Re-increasing dose²	% of dose reduction
450	36	150	6	300	33
600	30	150	6	300	50
750	18	375	12	600	20
750	18	375	12	600	20
600	34	150	2	300	50
600	24	0	18	150	75
150	24	0	12	75	50
300	36	0	12	150	50

Time is given in months, and dose in mg.¹Period with lower dose: length of time during which the patient tolerated the lower OMA dose.²Re-increasing dose: final dose administered with the patient remaining stable. The follow-up period after the dose reduction ranged between 18 and 36 months (data not shown in the table).