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Zenon Siergiejko, Ewa Świebicka, Nicola Smith, Clare Peckitt, Jo Leo, Guy Peachey & Robert Maykut

To cite this article: Zenon Siergiejko, Ewa Świebicka, Nicola Smith, Clare Peckitt, Jo Leo, Guy Peachey & Robert Maykut (2011) Oral corticosteroid sparing with omalizumab in severe allergic (IgE-mediated) asthma patients, Current Medical Research and Opinion, 27:11, 2223-2228, DOI: 10.1185/03007995.2011.620950

To link to this article: <http://dx.doi.org/10.1185/03007995.2011.620950>



Published online: 21 Sep 2011.



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Original article

Oral corticosteroid sparing with omalizumab in severe allergic (IgE-mediated) asthma patients

Zenon SiergiejkoRespiratory System Diagnostics and Bronchoscopy
Department, Medical University of Białystok, Poland**Ewa Świebocka**

University Children's Hospital, Białystok, Poland

Nicola Smith**Clare Peckitt****Jo Leo****Guy Peachey**Novartis Horsham Research Centre, Horsham,
West Sussex, UK**Robert Maykut**

Novartis Pharma AG, Basel, Switzerland

Address for correspondence:Zenon Siergiejko, Ogrodowa 5, 15-010 Białystok,
Poland.
Tel.: +48 601 896 534; Fax: +48 856 642 002;
siergiejko@csk.pl**Keywords:**Allergic asthma – Immunoglobulin E – Omalizumab –
Oral corticosteroidAccepted: 2 September 2011; published online: 21 September 2011
Citation: Curr Med Res Opin 2011; 27:2223–28**Abstract****Background:**

Long-term oral corticosteroid (OCS) therapy and related adverse events are associated with a significant burden on patients and healthcare resources.

Methods:

This subgroup analysis of a randomized, open-label, parallel-group study evaluated the OCS-sparing effect of omalizumab (OMA) added to optimized asthma therapy (OAT), compared with OAT alone. Patients (12–75 years) with severe allergic asthma, uncontrolled despite GINA 2004 Step 4 therapy, received OMA or OAT for 32 weeks. The change from baseline in OCS use by Week 32 in patients requiring maintenance OCS at baseline was assessed in terms of percent OCS dose change and numbers of patients with reduced/stopped or maintained/increased OCS.

Results:Eighty-two patients were receiving maintenance OCS at baseline (OMA/OAT $n=59$, OAT $n=23$). Change from baseline in mean maintenance OCS dose at Week 32 was significantly greater in the OMA/OAT group compared with the OAT group (-45% vs. $+18.3\%$, $p=0.002$). In the OMA/OAT group, 37 patients (62.7%) reduced/stopped OCS use at Week 32, compared with seven patients (30.4%) receiving OAT ($p=0.013$). Improvements in other efficacy outcomes were seen at Week 32 in the OMA/OAT group, irrespective of OCS use. An investigator global evaluation of treatment effectiveness at Week 16 was an effective predictor of persistent treatment response at 32 weeks for the majority of OMA/OAT patients (93%), also irrespective of OCS use.**Conclusion:**

In this open-label study of patients with severe allergic asthma, OMA/OAT therapy reduced maintenance OCS use, compared with OAT alone. Improvements in efficacy measures were observed in the OMA/OAT group, irrespective of OCS change.

Clinicaltrials.gov identifier:

NCT00264849.

Introduction

Approximately 5% of asthma patients have severe disease, which is often inadequately controlled by inhaled corticosteroids (ICS) and long-acting β_2 -agonists (LABA)¹. Long-term oral corticosteroid (OCS) therapy can achieve control in some patients with severe allergic asthma, but is associated with a significant burden on patients and healthcare resources as a result of deleterious adverse events (AEs). Steroid-sparing therapies are therefore pivotal to reduce the impact of OCS-associated AEs².

Omalizumab (OMA), a humanized anti-immunoglobulin E (IgE) monoclonal antibody with established efficacy and safety, is approved for the treatment of adults and adolescents with inadequately controlled severe (EU) or moderate-to-severe (US) allergic (IgE-mediated) asthma^{3–7}. In the EU, the indication has recently been extended to include children (6–<12 years) with severe allergic (IgE-mediated) asthma⁶. Several clinical trials support the efficacy of adjunctive OMA, as demonstrated by reductions in exacerbations and healthcare utilization, and improvements in lung function and asthma symptoms in patients with uncontrolled allergic asthma^{3–4,8–12}. Furthermore, OMA has also been shown to reduce the need for maintenance OCS in adults and adolescents in real-life practice^{13,14}.

The physician's global evaluation of treatment effectiveness (GETE) following 16 weeks of OMA therapy has been shown to be the most meaningful measure of response to OMA therapy¹⁵. The EXALT study (IGE025A2425) was designed to provide further support to the EU-label recommendation that clinical response to OMA should be assessed after 16 weeks of therapy, by evaluating the persistency of treatment response. The main EXALT study analysis⁸ demonstrated persistency in treatment response to add-on OMA from 16 to 32 weeks, based on the investigator's GETE, in patients with severe allergic asthma.

To test the hypothesis that the persistency of response to OMA would be reflected by a reduced need for maintenance OCS, we evaluated the OCS-sparing effect of OMA along with efficacy variables and AEs in patients enrolled in the EXALT study.

Methods

Patients

Patients were male or female aged 12–75 years with severe persistent allergic (IgE-mediated) asthma that was inadequately controlled despite treatment with high-dose ICS (>1000 µg beclomethasone dipropionate [BDP]/day or equivalent) and a LABA. Inadequate control was defined according to the Global Initiative for Asthma (GINA) 2004 Step 3 or 4 clinical features due to asthma¹. Details of the inclusion and exclusion criteria are described elsewhere⁸. This analysis is based on patients in the modified intention-to-treat (mITT) population who required maintenance OCS throughout the run-in phase and at baseline. It should be noted that the total population from the main EXALT study was stratified by OCS use, making it a valid subpopulation for analysis. The EXALT study was designed, implemented and reported in accordance with Good Clinical Practice, local regulations, and the ethical principles of the Declaration of Helsinki. The protocol and

informed consent forms were reviewed and approved by Institutional Review Boards and/or Ethics Committees. Written, informed consent was provided by patients, parents or a legally acceptable representative.

Study design

The EXALT study was an international, multicenter, randomized, open-label, parallel group study ($n=404$); full details can be found elsewhere⁸. Following a 1-week screening phase to determine eligibility (during which patients were required to have been receiving ≥ 800 µg BDP/day and a LABA), patients commenced an 8-week run-in phase prior to randomization. During run-in Weeks 1–4, asthma therapy was optimized according to the GINA 2004 guidelines¹, and Step 4 therapy was established. During the last 4 weeks of the run-in, no further dose adjustment to concomitant asthma controller medication was permitted. Patients must have continued to exhibit inadequate asthma control (defined according to GINA 2004 Step 3 or 4 clinical features¹) despite treatment with high-dose ICS (>1000 µg BDP/day or equivalent) and a LABA. In the main EXALT study patients were randomly assigned treatment in a 2:1 ratio in favor of OMA to allow a greater number of patients the opportunity to receive study treatment. The subset of patients requiring maintenance OCS therapy in the present analysis reflects this randomization ratio. During the 32-week study period, changes in doses of ICS and OCS were permitted if clinically appropriate. Dose adjustments were made according to best clinical practice, with decreases in dosage of both ICS and OCS made gradually.

Study assessments

In this pre-specified subgroup analysis, the main efficacy variable was the change from baseline in OCS use observed in patients receiving optimized asthma therapy (OAT) alone or OMA combined with OAT (henceforth referred to as OMA/OAT), following 32 weeks of therapy; in terms of percentage OCS dose change and numbers of patients with reduced/stopped or maintained/increased OCS.

The following efficacy variables were also analyzed in the patients receiving OMA/OAT or OAT who reduced/stopped or maintained/increased OCS use by Week 32. (These efficacy variables were not pre-specified and were analyzed post-hoc to assist a health authority request.)

- change from baseline in percentage predicted forced expiratory volume in 1 s (FEV₁) at Weeks 16 and 32;
- clinically significant asthma exacerbations (defined as worsening of asthma requiring treatment with rescue systemic [oral or intravenous] corticosteroids) over the 32-week treatment period;

- total visits (combined hospitalizations, emergency room [ER] visits and unscheduled outpatient [non-ER] clinical visits) due to asthma exacerbation over the 32-week treatment period;
- change from baseline in Asthma Control Questionnaire (ACQ) overall score at Week 32;
- change from baseline in night-time awakenings at Week 32;
- persistency rate (%) of response at Week 32, based on the investigator's GETE. Full details are described in detail elsewhere⁸.

AEs were recorded for each OCS use subgroup during the 32-week treatment period.

Statistical analyses

The population examined in this study were those in the mITT population (all randomized patients who had at least one post-baseline efficacy assessment) who required maintenance OCS throughout the run-in period and at baseline, according to the following subgroups:

- patients who reduced/stopped OCS by Week 32;
- patients who maintained/increased OCS by Week 32.

Patients were analyzed according to the treatment they received. The percentage and absolute changes in OCS dose from baseline by Week 32 were analyzed using a Wilcoxon rank-sum test. The number of patients stopping or reducing OCS by the end of study was analyzed using Fisher's exact test. Summaries of percentage predicted FEV₁ were presented for baseline and Week 32. Predicted FEV₁ was calculated using the Crapo formula. The rate of clinically significant asthma exacerbations and the combined rate of hospital admissions, ER visits and non-ER clinical visits due to asthma exacerbation during the 32-week treatment phase were analyzed using Poisson regression via generalized estimating equations. Descriptive statistics by the OCS use subgroup were reported for ACQ overall score and night-time awakenings at baseline and Week 32. Persistency rates were presented as a point estimate and 95% confidence interval (CI).

Results

Baseline characteristics

Eighty-two patients (OMA/OAT, *n* = 59; OAT, *n* = 23) were receiving maintenance OCS during the run-in and at baseline. Patient demographic and background characteristics were similar between treatment groups (Table 1) and compared with the overall study population⁸.

Table 1. Baseline demographic and clinical characteristics (modified ITT population: patients requiring maintenance OCS at baseline).

	OMA/OAT (<i>n</i> = 59)	OAT (<i>n</i> = 23)
Age, years		
Mean (SD)	45.2 (12.56)	45.6 (10.33)
Age distribution, years, <i>n</i> (%)		
12–17	1 (1.7)	0
18–54	41 (69.5)	17 (73.9)
55–64	14 (23.7)	5 (21.7)
≥65	3 (5.1)	1 (4.3)
Sex, <i>n</i> (%)		
Female	40 (67.8)	14 (60.9)
Weight, kg		
Mean (SD)	76.1 (19.63)	72.6 (16.70)
Serum total IgE, IU/mL		
Mean (SD)	206.7 (140.50)	274.9 (167.93)
FEV ₁ % predicted at baseline		
Mean (SD)	61.3 (13.64)	60.7 (11.72)
Number of clinically significant asthma exacerbations in last year prior to baseline		
Mean (SD)	2.7 (1.55)	3.3 (1.82)
Number of ER visits in last year prior to baseline		
Mean (SD)	1.0 (2.03)	0.7 (1.37)
Number of hospitalizations in last year prior to baseline		
Mean (SD)	0.5 (0.79)	0.7 (1.18)
Night-time awakenings in past 2 weeks prior to baseline		
Mean (SD)	7.93 (5.63)	7.96 (6.01)

All patients were Caucasian.

ER, emergency room; IgE, immunoglobulin E; ITT, intention-to-treat; SD, standard deviation.

Table 2. OCS use in patients receiving OMA/OAT and OAT (modified ITT population: patients requiring maintenance OCS at baseline).

	OMA/OAT (<i>n</i> = 59)	OAT (<i>n</i> = 23)	<i>p</i> value
OCS dose* at baseline, mean (SD)	13.1 (9.20)	12.8 (10.71)	
OCS dose* at Week 32, mean (SD)	8.4 (12.08)	15.1 (13.26)	
Change from baseline, % (SD)	–45.0 (50.22)	18.3 (85.13)	0.002†

*Prednisolone equivalent mg/day.

†Based on the Wilcoxon rank-sum test comparing OMA vs. OAT. ITT, intention-to-treat; SD, standard deviation.

Efficacy

The reduction from baseline in mean maintenance OCS dose at Week 32 was significantly greater in the OMA/OAT group compared with the OAT group (*p* = 0.002; Table 2). In the OMA/OAT group, 37 patients (62.7%) reduced/stopped OCS use at Week 32 compared with seven patients (30.4%) receiving OAT (*p* = 0.013; Figure 1). Eighteen and four patients (30.5% and 17.4%) reduced OCS use, and 19 and three patients (32.2% and 13.0%) stopped OCS use at Week 32, in the OMA/OAT and OAT groups, respectively (Figure 1).

In the OMA/OAT group, all patients who stopped OCS by Week 16 were still not using OCS at Week 32. For the 32 patients with maintained/increased OCS dose by Week 16, six had stopped and seven had reduced their OCS dose by Week 32. The majority of patients in the OAT group recorded maintained/increased OCS use at Week 16 and Week 32, 65.2% and 69.6%, respectively. At Week 32, similar efficacy outcomes were observed in the OMA/OAT group, irrespective of change in OCS use (Table 3).

The persistency rate of response in patients receiving OMA, based on the investigator's GETE, was similar to that observed in the original study population⁸. An investigator GETE at Week 16 was an effective predictor of persistent treatment response at Week 32 for the majority of OMA patients (93.5%). The persistency rate of response in patients who reduced/stopped or maintained/increased OCS use at Week 32 was 95.7% (95% CI: 87.3–100.0%) and 87.5% (95% CI: 64.6–100.0%), respectively. The

number of responders at Week 16 was greater in patients with reduced/stopped OCS use (23/37; 62.2%) compared with maintained/increased OCS use (8/22; 36.4%).

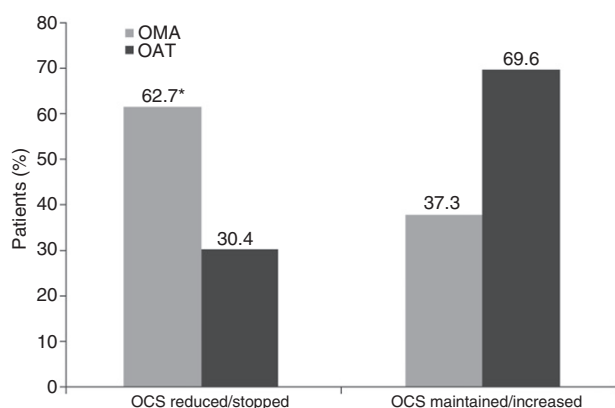
Safety

The majority of AEs were mild or moderate in patients requiring maintenance OCS at baseline, full details of reported AEs in the larger original population can be found elsewhere⁸. More patients in the OAT group reported severe AEs. Two patients reported severe arthralgia in the OMA/OAT group who reduced/stopped OCS. All other severe AEs were reported by no more than one patient in any treatment group.

Discussion

This analysis was designed to evaluate the OCS-sparing effect of add-on OMA in patients requiring maintenance OCS. Patients randomized to OMA/OAT had a greater reduction in maintenance OCS dose from baseline at 32 weeks than those on OAT alone ($p = 0.002$). In addition, nearly one-third of patients in the OMA/OAT group were able to completely stop maintenance OCS use. Improvements in other efficacy outcomes were seen at Week 32 in the OMA/OAT group, irrespective of OCS subgroup, supporting the previously demonstrated efficacy of adjunctive OMA therapy^{3–4,8–12}. Most AEs in this subset of patients requiring OCS at baseline were mild or moderate in severity. Of note, no cases of anaphylaxis were reported.

The main limitation of this investigation is that, as an open-label study, patients knew which treatment they were being given. The improvement in OCS usage in patients receiving OAT alone may relate to a 'Hawthorne effect' whereby patients participating in the trial exhibit better outcomes perhaps through improving



* $p = 0.013$ (OMA/OAT vs. OAT); based on Fisher's exact test for the number of patients achieving stopped/reduced OCS use vs. maintained/increased OCS use.

Figure 1. Change in OCS use in patients receiving 32-weeks' OMA/OAT and OAT.

Table 3. Efficacy outcomes at Week 32 in patients receiving OMA/OAT and OAT (modified ITT population: patients requiring maintenance OCS at baseline).

	OCS reduced/stopped		OCS maintained/increased	
	OMA/OAT (n = 37)	OAT (n = 7)	OMA/OAT (n = 22)	OAT (n = 16)
Mean change from baseline in FEV ₁ % predicted, % (SD)*	+6.8 (17.24)	−3.8 (14.84)	+2.0 (20.44)	+2.1 (16.95)
Mean number of clinically significant asthma exacerbations†	1.04	1.52	0.85	2.08
Mean number of combined visits/hospitalizations†	0.64	1.06	0.85	1.48
Mean change from baseline in ACQ overall score (SD)*	−0.96 (1.11)	+0.54 (0.59)	−0.65 (1.24)	+0.16 (0.95)
Mean change from baseline in the number of night-time awakenings in past 2 weeks (SD)*	−4.28 (6.01)	−0.25 (11.44)	−4.79 (6.60)	−3.38 (6.83)

*Following 32-weeks therapy.

†During the 32-week treatment period.

ITT, intention-to-treat; FEV₁, forced expiratory volume in 1 s; SD, standard deviation; ACQ, asthma control questionnaire.

their own management and involvement in care¹⁶. This may have altered their perception of symptoms which, in turn, may have influenced the physician's assessment of their need for continuing asthma maintenance therapy, introducing inadvertent bias into the outcome assessment. Although the publication of the main EXALT study acknowledged that analyses were based on open-label data and as such may be associated with physician and/or patient bias, it was also noted that the EXALT study mirrored real-world clinical practice with regard to the use of OMA⁸. Accordingly, the proportion of OMA/OAT patients who were able to reduce or stop maintenance OCS therapy and the size of OCS dose reduction in this analysis is of a similar magnitude to those reported in a pooled analysis of real-life data from French and German patients ($n = 346$) receiving OMA for severe persistent allergic asthma¹⁴. In the pooled study, of those patients receiving OCS at baseline ($n = 102$), 50.6% reduced or stopped OCS use after 16 weeks of OMA therapy (20.5% stopped; 30.1% reduced). Furthermore, in those patients who reduced/stopped maintenance OCS, baseline daily OCS dose (22.8 mg prednisolone equivalent) was reduced by a mean of 15.4 mg (74.3%)¹⁴. Similarly, trends towards reduced exacerbations and reduced healthcare utilization reported here reflect those observed before and after commencement of OMA in real-life studies^{14,17}.

The reduction in OCS use following OMA compares favorably with alternative add-on therapy in patients with severe asthma. The addition of anti-leukotrienes to ICS can improve asthma control, although the OCS-sparing effect is minimal¹⁸. The minimal OCS-sparing effect of leukotriene receptor antagonists (LTRAs) is also supported by the results of this study. Approximately half of each treatment group in this subgroup analysis were receiving a LTRA both prior to entry into the study and during the 32-week treatment period; it is therefore unlikely that LTRA use would have influenced the greater OCS-sparing effect demonstrated in the OMA treatment group. Experimental drugs such as methotrexate, cyclosporin or azathioprine, which may have an OCS-sparing effect, have failed to demonstrate an acceptable risk:benefit ratio^{19–21}.

The small number of patients included, particularly those in the OAT group is also a limitation of this analysis. Between treatment-group comparisons, relating to reduction in OCS use should be treated with caution. While reported for completeness, comparisons of other efficacy outcomes are less meaningful.

Conclusion

To conclude, this study shows that after 32 weeks of treatment with OMA/OAT, 63% of patients receiving

maintenance OCS at baseline reduced or stopped OCS use compared with 30% of patients in the OAT group. This improved OCS-sparing effect with OMA/OAT is consistent with previously reported studies of OMA as adjunctive asthma therapy^{13,14,22–24}. The study also demonstrated that use of an investigator GETE was an effective tool to predict treatment response, irrespective of OCS group^{8,15}. Improvements in efficacy measures were observed in patients treated with OMA as an add-on to OAT, irrespective of OCS change.

Transparency

Declaration of funding

The study was sponsored by Novartis Pharma AG. The authors were assisted in the preparation of the manuscript by Gary Cotter (ACUMED). Writing support was funded by the study sponsor.

Nicola Smith^c
Clare Peckitt^c
Jo Leo^c
Guy Peachey^c
Robert Maykut^d

Declaration of financial/other relationships

Z.S. has participated in Advisory Board Meetings and receives fees from Chiesi Pharmaceuticals. He holds no stock or other equities in pharmaceutical companies. E.Š. has disclosed that she has no significant relationships with or financial interests in any commercial companies related to this study or article. NS, CP, J.L, RM and GP are all employees of Novartis.

CMRO peer reviewers have disclosed any relevant financial information to the Editors.

Acknowledgements

Novartis provided financial support for the conduct of this research, and was involved in designing the studies, collecting, analyzing and interpreting the study data, writing the study reports, and the decision to submit this paper for publication.

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