Effectiveness of omalizumab in severe persistent asthma under real-life conditions

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Brusselle G, Michils A, Louis R, Dupont L, Van de Maele B, Delobbe A, et al. "Real-life" effectiveness of omalizumab in patients with severe persistent allergic asthma: the PERSIST study. *Respir Med* 2009;103(11):1633-42. Epub 2009 Jul 19.

Clinical question

Is omalizumab (a recombinant monoclonal antibody designed to treat immunoglobulin E [IgE]–mediated disease) an effective add-on treatment under real-life conditions for patients with severe persistent allergic asthma?

Type of article and design

The PERSIST study was a prospective, open-label, observational, multicentre study conducted in Belgium. The objective of this study was to determine the effectiveness of omalizumab as an add-on therapy in a real-life setting, with heterogeneous patients, environments, and physicians.

Selected physicians in Belgium were asked to enrol all their patients treated with omalizumab in the study. Omalizumab inhibits the binding of IgE to high-affinity receptors on pro-inflammatory cells and is indicated for patients with elevated IgE levels. It is administered by subcutaneous injections. Dose of omalizumab is calculated based on the patient's weight and baseline IgE serum level. All patients provided written informed consent. Patients were all deemed to have poorly controlled asthma despite taking high-dose inhaled corticosteroids (ICSs) and long acting β_2-agonists (LABAs), and fulfilled various inclusion criteria, including the Belgian reimbursement criteria for omalizumab approval.[1] Patients had 3 health care visits, which were also the routine visits required by the Belgian reimbursement criteria.[1] The first visit was the baseline patient assessment in which the use of health care services in the past year was recorded historically. The second visit occurred at week 16 after initial treatment when patients were reassessed to determine whether they would continue with the treatment based on the scientific leaflet and Belgian reimbursement criteria. The final visit occurred at week 52. There were no other study-related assessments beyond week 52.

Patients had to complete the Juniper Asthma Quality of Life Questionnaire (AQLQ)[2] at baseline and at weeks 16 and 52, and the European Quality of Life 5-Dimensions (EQ-5D) questionnaire at baseline and at week 52. The results were compared with baseline for any clinically meaningful improvement after treatment initiation.

Physicians also had to complete the Global Evaluation of Treatment Effectiveness (GETE) scale to describe a patient's response at week 16 and week 52. Concomitantly, the physicians had to determine whether there was improvement in the 2005 Global Initiative for Asthma (GINA) classification,[3] looking at daytime and nocturnal asthma symptoms and records of forced expiratory volume in 1 second.

Furthermore, the number of exacerbations and specific use of health care services were recorded longitudinally during the study and compared with the patient's history in the 12-month period before treatment.

The GINA classification, the GETE rating, and the AQLQ total and subscores had to be reported in order for the patient to qualify for the reimbursement program.

Relevance to family medicine

Family physicians are often the first caregivers to initiate and to modify the pharmacologic treatment among patients with asthma, with a mandate to optimize treatment in the long term. Although there are clear guidelines on pharmacologic management for patients with asthma, many family physicians are not comfortable moving beyond step 4 of treatment as indicated in the GINA guidelines[3]: the use of medium- to high-dose ICS with the addition of a LABA. Unfortunately, many patients remain poorly controlled despite such treatment. Step 5 in the current GINA guidelines suggests adding either an oral glucocorticoid or an anti-IgE treatment to step 4[3]—a strategy that is also highlighted in the Canadian Asthma Consensus Guidelines.[4] Given the innumerable side effects of systemic glucocorticoids, anti-IgE medication has become an interesting option as an add-on therapy. At the present time, there is a need for studies that describe the effectiveness of omalizumab under conditions that mimic real-life settings.

Overview of study outcomes

The primary objective of the PERSIST study included the determination of the effectiveness of omalizumab at 16 and 52 weeks as an add-on therapy, as well as to evaluate its safety and tolerability. A secondary objective was to evaluate patterns in the use of health care services during the 52-week treatment period compared with the preceding 12-month period.

The effectiveness of omalizumab was measured by questionnaires completed by the treating physicians and

patients. Comparison was also made of the number of exacerbations and the use of health care services experienced by patients before and after treatment.

The AQLQ completed by patients at weeks 16 and 52 and the EQ-5D questionnaire completed at week 52 were compared with baseline evaluations. Any improvement above or equal to 0.5 and 0.074 was deemed clinically meaningful improvement for the AQLQ and EQ-5D, respectively.

The GETE rating and the GINA classification determined by the physician at weeks 16 and 52 were compared with baseline data.

Furthermore, the number of exacerbations and specific use of health care services during the course of treatment were compared with historical data during the 12-month period before treatment initiation. The authors used the 0.605 INNOVATE (Investigation of Omalizumab in Severe Asthma Treatment) responder proportion (65% of patients receiving omalizumab in the INNOVATE trial received a rating of excellent or good on the investigator global evaluation)[5] to calculate that the sample size of PERSIST would detect such a proportion, and a 95% CI with a precision of plus or minus 0.077 and plus or minus 0.107 at 16 and 52 weeks, respectively. Intent-to-treat (ITT) data are presented in this appraisal; data on all patient visits are available.

Results

A total of 158 patients from 35 centres were included in this study. All the patients had high IgE levels (median 317 IU/mL, range 142.5 to 661.0 IU/mL) at baseline, with poorly controlled asthma while being treated with high-dose ICSs and LABAs.[1] Moreover, at baseline, 63.3% were using oral corticosteroids as an add-on therapy. Other add-on therapies included leukotriene antagonists, anticholinergics, theophylline, and antihistamines. Almost 71% of patients reported daily asthma symptoms, and on average experienced 2.67 severe exacerbations in the 12 months before treatment.

At 16 weeks, 37.9% of the ITT group were deemed to have shown improvement in the GINA classification,[3] 82.4% had good or excellent GETE ratings ($P<.001$), and 82.3% had a greater than or equal to 0.5-point improvement on the 7-point AQLQ ($P<.001$). Furthermore, about 91% of patients also remained exacerbation free ($P<.001$).

At 52 weeks, the ITT sample comprised 130 patients: 31% improved in the GINA classification[3] ($P<.005$); 72.3% had good or excellent GETE ratings ($P<.001$); 65.6% remained exacerbation free; and 84.4% had a greater than or equal to 0.5-point improvement on the AQLQ ($P<.001$). Only 51.5% of the ITT population had comparative EQ-5D data, but there was a significant increase in general health ($P<.001$). Almost 66% of patients had fewer health care visits (mean [SD] reduction of 1.49 [7.56]; $P<.001$).

Of note, with omalizumab as an add-on therapy, 18.5% of patients had discontinued methylprednisolone, and there was a 39.4% reduction in average daily dose of methylprednisolone. Overall, 55.6% of patients experienced at least 1 side effect and 12% of patients had discontinued omalizumab owing to these effects.

Analysis of methodology

Being a prospective, open-label, observational study without a placebo arm makes interpretation and application of study findings difficult in some ways. It is not apparent whether the treating physicians were specialists or generalists and whether real-life management of severe asthma in Belgium is comparable to other countries including Canada. Using the 0.605 INNOVATE responder proportion, the sample size of the PERSIST study provided a robust precision calculation—a feature that bolsters data interpretation in the absence of a placebo arm. The authors appropriately state that more research is needed to validate their findings related to physician-rated effectiveness, improvements of quality of life, exacerbation rates, and use of health care services—changes that were greater than in other recent studies with omalizumab.[5]

It is relevant to note that the duration of the study provided adequate time to monitor important end points such as severe exacerbations, safety, and use of health care services.

Application to clinical practice

Despite some important design limitations, the PERSIST study describes impressive improvements in several clinically relevant end points when omalizumab is used as add-on therapy in severe persistent asthma. These findings are consistent with results of randomized placebo controlled trials evaluating omalizumab in severe asthma.[6,7] Given the ambiguity around how real-life care in Belgium is defined, application of these findings to the primary care setting remains difficult. Given that many cases of severe persistent asthma among patients remain uncontrolled, and that these patients are often cared for by family physicians, effective alternative therapies are needed. The high cost of omalizumab will dictate the need for appropriate assessment of patient response to an initial trial of therapy. The extensive experience of omalizumab use by one of the authors (A.D.D) suggests that management of severe persistent asthma in primary care, including the use of omalizumab, will likely require well defined collaborative relationships between patients and primary and specialty caregivers. Primary care physicians who are not familiar with how this drug is administered in the office setting, including the risk of allergic reaction, should refer patients to specialists.

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Competing interests
Dr D'Urzo has received research, consulting, and lecturing fees from GlaxoSmithkline, Sepracor, Schering-Plough, Altana, Methapharma, AstraZeneca, ONO Pharmaceutical, Merck Canada, Forest Laboratories, Novartis, Boehringer Ingelheim Ltd, Pfizer Canada, SkyePharma, and KOS Pharmaceuticals.

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BOTTOM LINE

- The PERSIST study reported improvements in several clinically relevant asthma-control end points when omalizumab was used as an add-on therapy among patients with severe asthma during a 52-week period.
- Ambiguity regarding how real-life asthma care is defined in Belgium might limit generalization of study findings to other settings.
- The use of a responder proportion from a previous controlled trial involving omalizumab to calculate study precision might bolster data interpretation in the absence of a placebo arm; however, the latter is an important weakness of this study.
- Well defined collaborative relationships between primary and specialty caregivers could promote identification and optimal management of patients with severe persistent asthma who might be candidates for omalizumab therapy.

POINTS SAILLANTS

- Dans l'étude PERSIST, on a signalé plusieurs améliorations à des paramètres pertinents au contrôle de l'asthme lorsqu'on utilisait l'omalizumab en tant que thérapie auxiliaire chez des patients souffrant d'asthme sévère durant une période de 52 semaines.
- Une certaine ambiguïté entourant la définition des soins réels pour l'asthme en Belgique pourrait limiter la généralisation des constatations de l'étude à d'autres milieux.
- L'utilisation d'une proportion de répondants tirée d'une étude contrôlée antérieure impliquant l'omalizumab pour calculer la précision de l'étude peut améliorer l'interprétation des données en l'absence d'un groupe témoin avec placebo; par ailleurs, cette absence représente une importante faiblesse de cette étude.
- Des relations de collaboration bien définies entre les médecins de soins primaires et les spécialistes pourraient favoriser l'identification et la prise en charge optimale des patients souffrant d'asthme sévère persistant qui pourraient être candidats à une thérapie à l'omalizumab.