Treball de recerca corresponent al Màster Oficial "INVESTIGACIÓ CLÍNICA APLICADA EN CIÈNCIES DE LA SALUT" (Convocatòria juny 2013)

"Induced sputum versus exhaled nitric oxide for the evaluation of airway inflammation in allergic paediatric asthma patients treated with omalizumab"

AUTOR: XAVIER DOMINGO MIRÓ
Llicenciat en Medicina i Cirurgia
Especialitat de Pediatria

DIRECTOR: Dr. CHRISTIAN DOMINGO
TUTOR: Dr. FERRAN SEGURA

Departament de Medicina
Facultat de Medicina
Universitat Autònoma de Barcelona

Línia de Recerca: Immunologia, al·lèrgia i malalties sistèmiques.
Keys words: omalizumab, severe asthma, induced sputum.
Paraules clau: omalizumab, asma greu, esput induït.
Any d'elaboració: 2012-2013

INDEX

SUMMARY

Our purpose is to determine the inflammatory changes in the airways of allergic paediatric asthma patients treated with omalizumab, measured by the percentage of eosinophils in induced sputum and exhaled nitric oxide (FENO). We observed a progressive and statistically significant decrease of eosinophil count in the induced sputum meanwhile FENO, although very sensible, was a less reproducible and thus a less reliable method to evaluate chronic airway inflammation in this population. Induced sputum seems to be a better method to monitor chronic inflammation and thus the response to chronic omalizumab treatment while FENO measurement would be more useful to monitor acute events preceding exacerbations.

RESUM

El nostre objectiu és determinar els canvis inflamatoris en la via aèria de pacients pediàtrics afectes d'asma al·lèrgica tractats amb omalizumab, mesurat pel percentatge d'eosinòfils en esput induït i la fracció d'òxid nítric exhalat (FENO). Hem observat una disminució progressiva i estadísticament significativa del percentatge d'eosinòfils en esput induït mentre que la FENO, tot i ser molt sensible, resulta ser un mètode menys reproductible i per tant menys fiable per avaluar la inflamació crònica de la via aèria d'aquesta població. L'esput induït sembla una millor tècnica per monitoritzar la inflamació crònica i així la resposta al tractament amb omalizumab. En canvi, la FENO sembla més útil per predir exacerbacions.

INTRODUCTION

The prevalence of allergic diseases has progressively increased in the past decades. Asthma is one of the most common chronic diseases worldwide, affecting an estimated 300 million individuals. The ISAAC study reported the prevalence in the paediatric population to be around 10%, affecting 9 million Americans < 18 (1). In our setting, the figure in the general population is around 3.5% (2).

Asthma management is a costly business, accounting for around 1-2% of the total health care expenditure in developed economies (3). Developing economies are also likely to face increased demand (3). Poorly controlled asthma is expensive, and investment in prevention medication is likely to yield cost savings in emergency care (3-4).

The incidence, morbidity and mortality of the condition have increased over the last fifty years despite the development of new drugs. Fewer than 1% of the asthmatic population are steroid-dependent, but these patients consume most of the time and resources (5). To address this situation, asthma units have been set up for severe chronic asthma and have proved effective and efficient (6).

The consensus documents published by professional societies all support a stepwise therapeutic approach for asthma (3, 7-8). The update of the Global initiative for asthma treatment (GINA) report (3) in November 2006 offered for the first time an alternative to oral corticosteroids in patients included in step V (the most severe patient's step). This drug is omalizumab, an anti-IgE blocking agent. To date, there is a huge experience on omalizumab effectiveness in adults (9), but in paediatric population, the information is fewer. Moreover, there is scarce information about the inflammatory response in paediatric asthma patients treated with omalizumab. Our aim was to study the changes the drug could cause in the airway inflammation in severe asthma patients.

MATERIAL AND METHODS

Population.

Patients were recruited from the out-patient clinic for asthma treatment of the paediatric service at our institution.

The inclusion criteria were:

1) Patients aged between 2 and 18 years.

2) Severe asthma according to the GEMA guide.

3) Positive prick test or in vitro reactivity (CAP) to at least one aeroallergen.

The exclusion criteria were:

1) Patient or patient's relatives refusing treatment

2) Hypersensitivity to omalizumab

3) Patient unable to regularly attend the asthma unit for control and drug administration

4) Previous anti-IgE treatment

5) Patient's relatives refusing to sign the written informed consent

Sample size: since this is one of the few studies including patients under 6 years treated with omalizumab, we could not calculate the number of patients needed for a post-hoc analysis. Following the experience in a large observational study in adult population (9), for statistical evaluation, we planned to have a minimum of 30 patients followed.

Methods:

Study design: Single-centre, prospective, open-label, observational interventional study.

Setting: The study will be performed at the Paediatric Service of Corporació Parc Taulí (CPT) (Sabadell/Catalonia), a 760-bed university teaching hospital.

Treatment protocol: best standard care (BSC) following the recommendations of the GEMA included inhaled corticoids, inhaled long-acting beta-agonists (LABA) (salmeterol 50 µg bid), montelukast and oral methyl-prednisolone if needed. Prior to starting omalizumab treatment, patients underwent a run-in period of at least one month to assess the patients was correctly following the BSC established for him.

The study was conducted between 2006 and 2012.

Outcomes: the primary outcome of effectiveness was the decrease in sputum eosinophil count. The secondary outcome was to study the changes in patients' FENO.

The primary safety outcome was to estimate tolerance drug and the incidence of side-effects.

Instrumentation

At entry we obtained from every patient: a total IgE concentration, specific IgE against the most relevant allergen, the percentage of eosinophils in a smear of induced sputum and the exhaled fraction of nitric oxide (FENO) (Niox Mino, Phadia). Induced sputum and NO were measured at the end of follow-up.

Intervention: Omalizumab was administered once or twice a month in the outpatient unit of the paediatric service of our institution. Patients remained under observation for one hour after all injections. The dose was calculated according to the dosing tables published and accepted by the European Medical Agency (EMEA) (10). If the calculated dose exceeded the highest allowed dose, the maximum allowed dose was administered.

Side-effects.

Patients were specifically asked about side-effects at each visit. They were also given the telephone number of the outpatient unit of the paediatric service to report any suspected side-effects. Immediate side-effects would have been detected at outpatient unit during the period of clinical observation.

Statistical analysis. Descriptive statistics will include frequencies and percentages for categorical variables and means and standard deviations for continuous variables. Parametric (student's t test for paired data) will be used to compare the initial and end, FENO and sputum induced cell count. SPSS will be used for data compilation and analysis. A p-value < 0.05 will be considered statistically significant

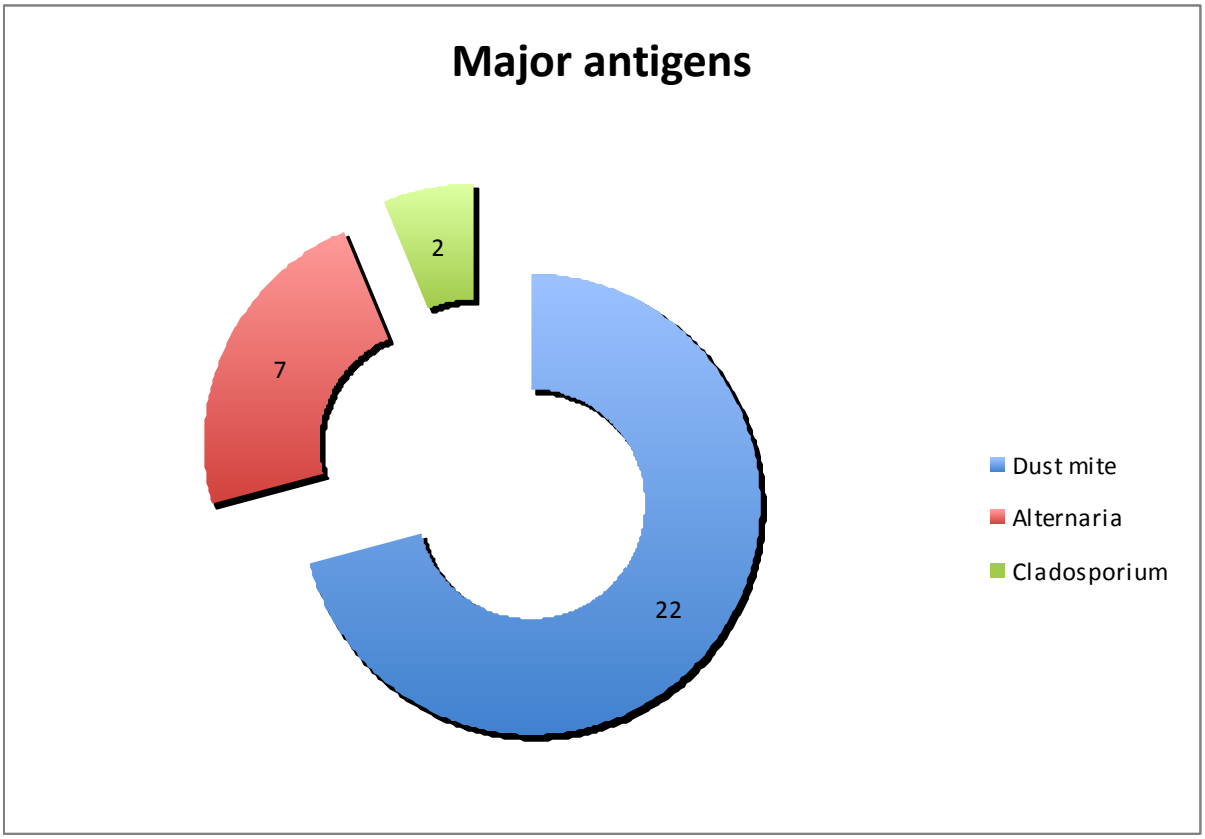
Informed consent. Written informed consent was obtained if age was under 6 years, since the treatment is only accepted by the international guidelines for older population. The IRB at our institution requires only oral informed consent from patients for the anonymous treatment of their data. The IRB of the hospital has accepted the study to be performed.

RESULTS

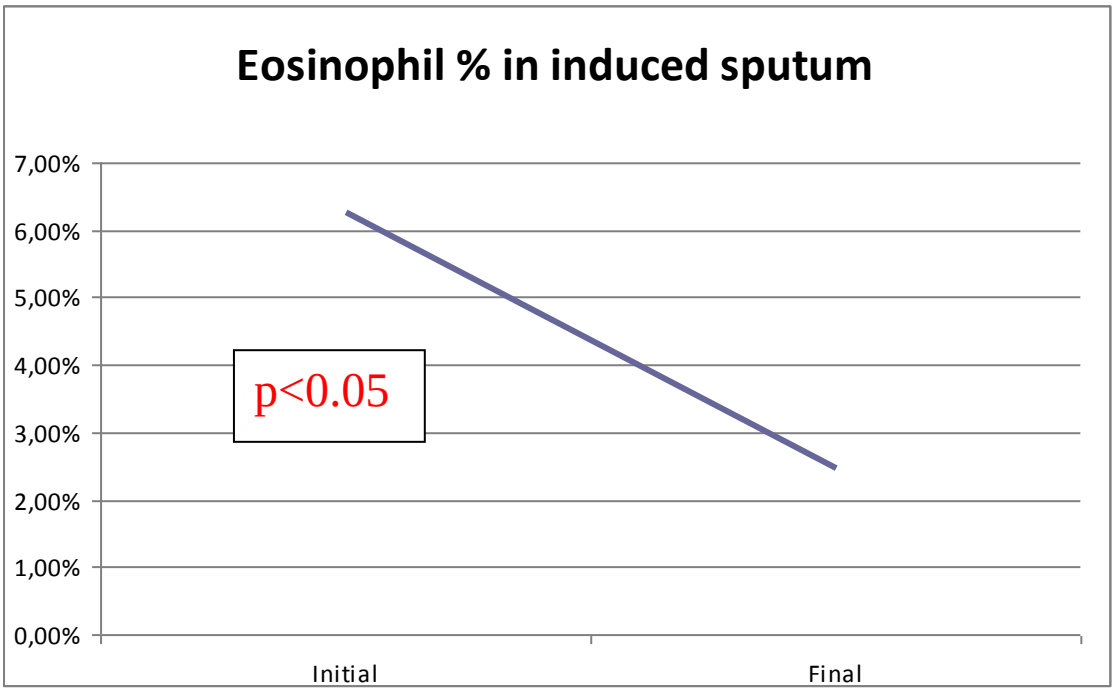
Between 2006 and 2012, 31 patients with asthma were treated with omalizumab (15 male -51.6%; 16 females -48,4%-). The age ranged between 6 -18 years. The follow-up of the patients was not uniform, ranging from 2 to 6 years.

Total IgE concentration at entry: 668.89 (117.79) IU/mL.

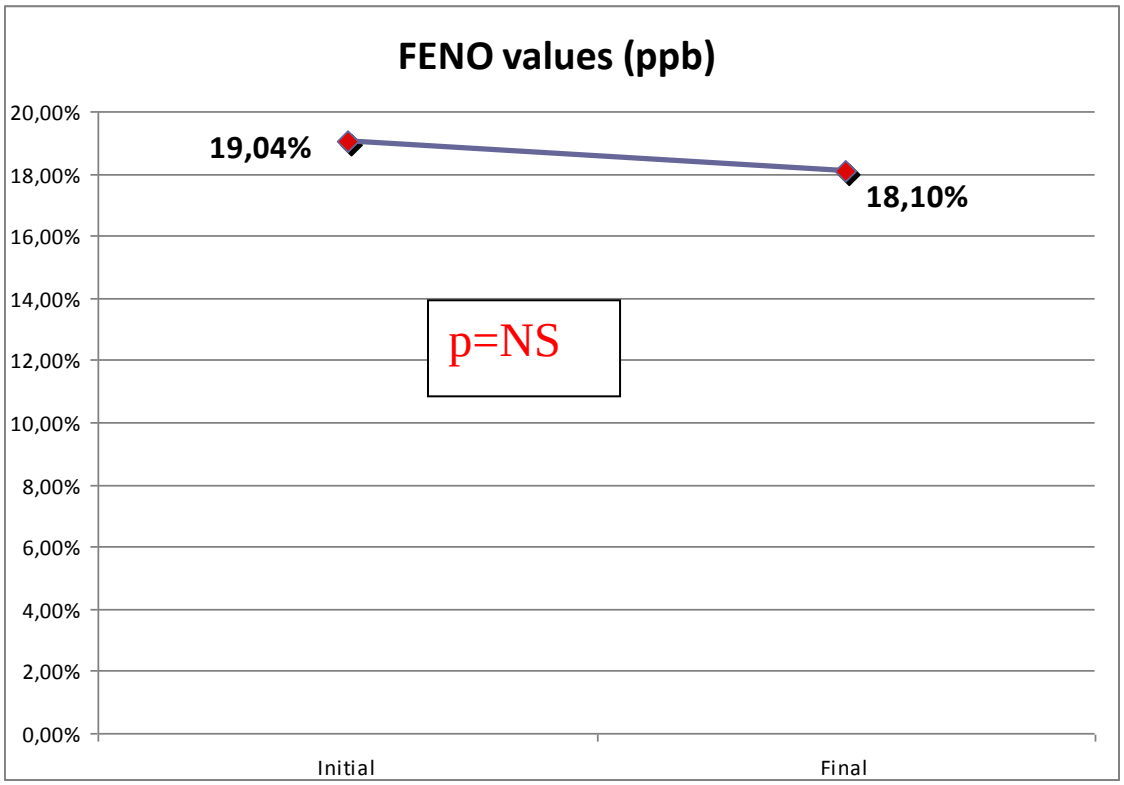
Specific IgE against the major antigen at entry: 42.15 (7.32) IU/mL; (22 house dust mite; 7 alternaria; 2 cladosporium).



Initial and end induced sputum: **6.26** (2.03) % Vs **2.47** (0.36) %; (p< 0.05).



Initial and end FENO values: 19.04 (1.98) ppb Vs 18.10 (2.11) ppb (p=NS). Three patients were excluded from the evaluation due to exaggerated values in the final NO measurement that preceded a severe exacerbation.



DISCUSSION

The prevalence of allergic diseases has progressively increased in the past decades. Asthma is one of the most common chronic diseases worldwide, affecting an estimated 300 million individuals. The ISAAC study reported the prevalence in the paediatric population to be around 10%, affecting 9 million Americans < 18 (1). In our setting, the figure in the general population is around 3.5% (2).

The consensus documents published by professional societies all support a stepwise therapeutic approach for asthma (3, 7-8). However, patients who require frequent or continuous oral corticosteroid administration have received little attention. Due to the severe side-effects of steroids when administered over long periods or at high doses, considerable efforts have been devoted to the search for a possible corticosteroid sparing agent and many drugs have been assessed (12). The update of the Global initiative for asthma treatment (GINA) report (3) in November 2006 offered for the first time an alternative to oral corticosteroids in patients included in step V (the most severe patient's step). This drug is omalizumab, an anti-IgE blocking agent. So far, omalizumab has mainly been used in moderate and severe asthma patients to quantify the inhaled corticosteroids (10) rather than the oral steroid-sparing capacity

The GINA advises the use of anti-IgE as an alternative or in addition to oral corticosteroids in step V patients and in uncontrolled patients with severe allergic disease and increased levels of IgE. In a naturalistic setting, omalizumab has shown and excellent tolerance and effectiveness in a population of patients with steroid-dependent asthma, the first study of its kind to date (9). Although the drug has been mainly used in adult population, to date there is already enough experience in paediatric population to

prescribe the drug. In any case anyway, there is a lack of parameters that allow the clinician when and how decrease or stop the treatment (13)

It is well known nowadays that asthma is a chronic inflammatory disease of the airways caused by the interaction of several types of cells and molecules. The cells involved include mast cells, eosinophils, T-lymphocytes, macrophages and neutrophils. The inflammatory cascade is mediated by cytokines and interleukins. When an atopic individual is exposed to an antigen, the dendritic cells (specialized macrophages located in the organism's epithelium) internalize it, process it and present it to a T lymphocyte, via the major histocompatibility complex. In this process the T lymphocyte develops a Th2 or a Th1 profile. When the type of antigen is an allergen, the lymphocyte differentiates into a Th2 cell able to produce IL-4 which in turn promotes the synthesis of IgE by the B lymphocytes (10).

IgE-dependent inflammatory phenomena have been studied in depth and are recognized in atopic subjects (14). In these subjects, exposure to high concentrations of allergens, above all dust mites at early ages, leads to a high concentration of serum IgE, which favours the appearance of allergic symptoms. Omalizumab has been found to block 99% of the circulating IgE in four hours (9). Nevertheless, the benefits of the treatment are slow to manifest themselves, and in some cases the patient may take several months to improve.

Omalizumab offers some delayed benefits. Some studies have demonstrated its anti-allergic and anti-inflammatory properties, such as the reduction in circulating and tissue eosinophils and, more recently, the increase in eosinophil apoptosis and the decrease in granulocyte macrophage colony stimulating factor (GM-CSF), IL-2 and Il-13 (14). Prussin et al's (15) results demonstrated that anti-IgE therapy causes a rapid decrease in

dendritic cell surface FcεRI expression and established that IgE is an important regulator of FcεRI expression by dendritic cells.

Omalizumab's effect in treated patients is progressive, and for this reason the time to response is not uniform. IgE directly binds to and activates receptors present on eosinophils, neutrophils, and monocytes. Thus, the free IgE concentration may also be a key factor in patient control. Two aspects are involved in this process: the duration of the inflammatory process, and the triggering factor, that is, the free IgE (9)

Though the regulation of IgE described above is found in atopic subjects, recent publications show that IgE may be produced by T lymphocytes in non-allergic subjects due to the presentation of the allergen through the mucosa. This IgE may bind to the high affinity receptors on the mast cells or basophils and produce the same type of inflammation as in the subjects considered allergic (10). The rationale for the use omalizumab in non-allergic patients is based in the relatively recent finding that IgE can be produced locally in mucosal tissue, without any increase in IgE levels in the blood, somewhat blurs the distinction between non-atopic and atopic diseases such as asthma (16)

In any case, clinicians lack of reliable parameters to monitor drug response other than spirometry and/or patient's clinical evaluation. The rationale of our study was that the evaluation of airway inflammation could offer some advantages to monitor drug response. In this way, we postulated that FENO as well as eosinophil count in induced sputum could be helpful parameters. We observed that the eosinophil count in induced sputum progressively decreased in treated patients, although the direct target of omalizumab is IgE. In other words, omalizumab showed an anti-eosinophil effect that could help to explain, at least partially the effect of the drug. FENO shows the airway inflammation in a cross sectional manner. It is influenced by many factors such as the

meteorological conditions, inhaled steroid treatment, that can acutely modify its airway concentration. Thus it is not surprising that this parameter is less reliable to monitor drug response in such a severe cohort of patients.

Our study has several limitations, the most important being its uncontrolled nature. This means that we could not compare a treated group with a control group. However, this could in fact be considered as a strength, since the study was performed in a naturalistic setting, which is the ideal way to demonstrate the results of an effectiveness study.

CONCLUSIONS

Omalizumab allowed a statistically significant decrease in the percentage of eosinophils in induced sputum of this cohort of patients. Although very sensible, NO is a less reproducible and thus less reliable method to evaluate chronic airway inflammation in a paediatric allergic population with uncontrolled severe asthma. Induced sputum seems to be a better method to monitor chronic inflammation and thus the response to chronic omalizumab treatment while NO measurement would be more useful to monitor acute events preceding exacerbations.

BIBLIOGRAPHY

1. - Asher I. ISAAC International Study of Asthma and Allergies in Childhood. Pediatr. Pulmonol. 2007; 42:100-110.

2. - Jaen A, Ferrer A, Ormaza I, Rue M, Domingo C, Marin A. Prevalence of chronic bronchitis, asthma and airflow limitation in an urban-industrial area of Catalonia. Arch. Bronconeumol. 1999; 35:122-128.

3. - www.ginasthma.com

4. - Domingo Ch, Ortún V. Chronic Saturation of Emergency Departments: They Should not Be Flooded by Patients With Chronic Diseases. Arch Bronconeumol 2006; 42: 257-9.

5. - Domingo Ch, Moreno A, Amengual M.J, Comet R, Luján M. Twelve years' experience with methotrexate for GINA treatment step 5 asthma patients. Curr Med Res Opin 2008; 25: 367-374. Doi:10.1185/03007990802643466.

6. - Domingo C. Effectiveness and efficiency of an outpatient clinic for corticosteroid-dependent asthmatics. Arch. Bronconeumol. 2001; 37: 274-280.

7. - International Consensus Report on diagnosis and treatment of asthma. National Heart, Lung and Blood Institute, National Institutes of Health. Bethesda, Maryland 20892. Publication number 92-3091, March 1992. Eur. Respir. J. 1992; 5:601-641.

8. - www.gemasma.com

9. - Domingo Ch, Moreno A, Amengual M.J, Montón C, Suárez D, Pomares J. Omalizumab in the management of oral corticosteroid-dependent ige-mediated asthma patients. Curr Med Res Opin. 2011; . 27: 1, 2011, 45–53. doi:10.1185/03007995.2010.536208

10. - Domingo Ch, Pacheco A, Hinojosa M, Bosque M. The Relevance of IgE in the Pathogenesis of Allergy: The Effect of an Anti-IgE Drug in Asthma and Other Diseases. Recent Patents Inflamm. Allergy Drug Discov. 2007; 1: 151-164

11. - Roca J, Sanchis J, Agusti-Vidal A, Segarra F, Navajas A, Rodriguez-Roisin R, et al. Spirometric reference values from a Mediterranean population. Bull. Eur. Physiopathol. Respir. 1986; 22: 217-224.

12. - Comet R, Domingo C, Larrosa M, Rue M, Amengual MJ, Marin A. Benefits of low weekly doses of methotrexate in steroid-dependent asthmatic patients. A double-blind, randomized, placebo-controlled study. Respir. Med. 2006 100: 411-419.

13. – Domingo C, Pomares X. Can omalizumab be effective in chronic eosinophilic pneumonia? Chest. 2013;143: 274. doi: 10.1378/chest.12-2035.

14. - Owen C.E. Immunoglobulin E: Role in asthma and allergic disease: Lessons from the clinic. Pharmacol. Ther. 2007; 113: 121–133.

15. - Prussin C, Griffith DT, Boesel KM, Lin H, Foster B, Casale TB. Omalizumab treatment downregulates dendritic cell Fc _R1 expression. J Allergy Clin Immunol. 2003;112:1147-54.

16.- Domingo C, Pomares X, Angrill N, Rudi N, Amengual MJ and Mirapeix RM. Effectiveness of omalizumab in non-allergic severe asthma. J Biol Regul Homeost Agents 2013; 27: 45-53.