

EFFECTIVENESS OF OMALIZUMAB IN THE TREATMENT OF CHRONIC RHINOSINUSITIS WITH NASAL POLYPS: SYSTEMATIC REVIEW

Tiago Soares Santos, MD

São Sebastião Hospital, Santa Maria da Feira, Portugal

Vítor F Certal, MD

São Sebastião Hospital, Santa Maria da Feira, Portugal

Center for Research in Health Technologies and Information Systems,

University of Porto, Portugal

Paulo Gonçalves, MD

Carlos Carvalho, MD

São Sebastião Hospital, Santa Maria da Feira, Portugal

Abstract

BACKGROUND: Omalizumab is a monoclonal anti-IgE antibody which reduces serum and tissue IgE levels blocking the inflammatory cascade. To date this drug has authorization for treatment of moderate-to-severe allergic asthma. The chronic rhinosinusitis with Nasal Polyps (CRSwNP) is a chronic inflammatory disease whose exact pathogenesis remains unknown. In most Caucasian patients CRS is associated with eosinophilic inflammation and local production of IgE. The aim of this systematic review was to evaluate the existing evidence on the use of omalizumab in CRSwNP.

MATERIALS AND METHODS: Searches were carried out in Medline, Scopus and Cochrane Library, followed by a detailed handsearch. The search was conducted from January 1990 to December 2013. Prospective and retrospective studies were included.

RESULTS: Four studies met the inclusion criteria for this systematic review: two randomized controlled trials, a retrospective case-control study and a case series. Omalizumab appears to improve both endoscopic evaluation and sinonasal inflammation, with an acceptable safety profile. However, the evidence level is low.

CONCLUSIONS: The evidence shows that the use of omalizumab may be an effective therapeutic alternative in CRSwNP, especially in patients with more aggressive forms of the disease, with surgical procedures history, and bronchial asthma. However, more randomized, placebo-controlled, double-blind studies with higher number of patients are still needed to determine the efficacy of anti-IgE treatment in CRSwNP.

Keywords: “Chronic Rhinosinusitis”, “Nasal Polyposis”, “Nasal Polyps”, “Omalizumab”, “Anti-IgE”

Introduction

Chronic Rhinosinusitis with Nasal Polyps (CRSwNP) is an inflammatory disease, whose exact etiology remains unknown, with an estimated prevalence in Europe’s adult population between 2 and 4 %⁽¹⁾. Researchers suggested that, if after the activation of the inflammatory cascade this inflammation persists, the consolidation of the stromal oedema may occur resulting in the formation of nasal polyps⁽²⁾. Recently it has been shown that, in most Caucasian patients, this nosological entity is characterized by local eosinophilic

inflammation with high production of immunoglobulin E (IgE), as well as interleukin-5 (IL-5) and eosinophilic cationic protein⁽³⁾.

When medical treatment is ineffective, surgery is an option for CRSwNP. However, recurrence rate is high especially in patients with concomitant asthma, and from these, those who show acetylsalicylic acid intolerance present an even higher rate⁽¹⁾. The concomitant existence of asthma and CRSwNP indicates a more severe respiratory inflammation, as well as higher levels of localized IgE^(4,5). As such, effective treatment is more complex in these patients.

Omalizumab (NovartisTM) is a monoclonal antibody, available since 2003 that selectively binds to the Fc region of human IgE reducing free IgE, as well as producing extensive anti-inflammatory effects with eosinophil apoptosis induction. This effect was established in sputum samples and bronchial biopsies of asthma patients⁽⁶⁾. Considering the pathological similarity between bronchial asthma and CRSwNP, with the presence of large eosinophilic infiltration, this drug has potential effectiveness in the treatment of CRSwNP.

Currently, omalizumab is approved for treatment of moderate-to-severe allergic asthma in patients six years-old or older⁽⁷⁾. Besides, there are also some anecdotal reports^(8,9) that mentioning omalizumab's effectiveness in CRS with polyps treatment in patients with concomitant asthma.

The purpose of this review was to systematically evaluate the existing published evidence on omalizumab's use in the treatment of CRSwNP.

Methods

Study Design

A systematic review of prospective and retrospective studies was performed in order to evaluate the effectiveness of omalizumab use in CRSwNP treatment.

The methodological approach included the definition of the search strategy and the articles quality evaluation.

Search Strategy

The method used to localize potentially eligible articles involved a search of literature in the following databases: Medline, Scopus and Cochrane Collaboration. The search included articles published since January 1st, 1990 (when the drug was registered in Food and Drug Administration - FDA) until December 31st, 2012. There was a language restriction on the articles which full text was written in Portuguese, English, Spanish, Italian and French, the key words being: "*rhinosinusitis*", "*nasal polyps*", "*nasal polyposis*", "*omalizumab*", "*anti-IgE*"; "*IgE*", "*treatment*".

An additional search was performed using the same strategy and including articles published until December 31st, 2013.

A review of the most important articles references was performed as well as a manual search of abstracts and contact with specialists developing research in this area.

Study quality assessment

Titles and abstracts found in databases were examined by two reviewers e selected in terms of relevance. Posteriorly, both reviewers independently analyzed the full text of the articles initially selected. All disagreements were settled by consensus.

Studies were included (prospective or retrospective), in which the effectiveness of omalizumab's use in CRSwNP treatment was objectively evaluated, through both nasal endoscopy or imaging exams, or subjectively by quality of life (QoL) evaluation tools.

Results

Database search and article selection

All database research was accomplished until 31 of January 2014. A flow chart of identification and selection process of the studies is shown in figure 1.

In total, 2073 articles were identified using the aforementioned database research strategies. After evaluation of all titles and abstracts according to relevance, 2046 were excluded (exclusion reasons are mentioned in figure 1). The remaining 27 articles' full texts were evaluated in a thorough manner. Of these, 22 articles⁽¹⁰⁻³¹⁾ were excluded as they did not display any objective or subjective outcome that evaluated CRSwNP. One article⁽³²⁾ was excluded for being written in Japanese. As such, this review includes 4 articles⁽³³⁻³⁶⁾.

Methodological Quality of the Included Articles

The main methodological features of the included articles are presented in table 1.

Only two of the four articles were randomized controlled trials (RCT)^(33,35), and the remaining were a retrospective case-control study⁽³⁴⁾ and a series of cases⁽³⁶⁾. All the studies had a small sample size (8 to 24 patients), and in two of them^(33,36) the selection criteria was not clearly defined. None of the RCT described any blinding strategies. Additionally, in two articles^(33,36) the administered drug dosages were not clearly defined, and, in one of these⁽³⁶⁾, the treatment time was also not defined. The follow-up time varied between 5 and 28 months.

Due the limited number of patients, a meta-analysis of the results was not performed.

Analyzed Variables

Nasal Polyps Endoscopic Score

All of the included articles evaluated the nasal polyps endoscopic score variation, both in pre and post omalizumab treatment. However, the staging system used was not the same in all studies (see table 1).

In three articles^(33,34,36) there was a statistically significant reduction between the pre and post omalizumab treatment endoscopic scores. However, only Gevaert, et al⁽³³⁾ showed statistical significance when patients treated with omalizumab were compared with the ones of the placebo group.

The study of Pinto, et al⁽³⁵⁾ concluded that no significant differences exist in none of the studied groups, although these results are not clearly reported.

Staging by Computerized Tomography

Two^(33,34) of the three articles that evaluated CT changes^(33,34,35) used the Lund-Mackay score to measure sinus inflammation treatment changes. In the remaining article, a quantitative system was used to evaluate CT sinuses opacification level, before and after treatment⁽³⁵⁾.

In all studies there was a CT evaluation score reduction when the pre and post-treatment values of the treated groups were compared, but Penn, et al⁽³⁴⁾ did not report statistically relevant differences. Gevaert, et al⁽³³⁾ reported a significant reduction of the Lund-Mackay score when comparing both groups (omalizumab vs. placebo) at the 16 weeks of omalizumab treatment (p=0,04).

Quality of Life Evaluation Tools

Quality of life evaluation tools were used only in the RCT. The used tool for general evaluation was the same in both papers (Short-form Health Questionnaire - SF-36). However, the specific CRS evaluation questionnaires were different in the two articles. Gevaert, et al⁽³³⁾ used the Rhinosinusitis Outcome Measuring Instrument (RSOM-31), but Pinto, et al⁽³⁵⁾ used the Sinonasal Outcome Test (SNOT-20).

General evaluation showed antagonistic results. On one hand, Pinto, et al⁽³⁵⁾ report none significant score reduction of any survey's dominions. On the other hand, Gevaert, et al⁽³³⁾ showed a significant score reduction before and after the omalizumab intervention on the treated group, but none on the placebo one.

In terms of the specific CRS evaluation surveys (RSOM-31 and SNOT-20), both studies reported statistically significant reductions in pre and post-treatment survey scores for the treated groups without any change in placebo ones.

Other Analyzed Variables

Pinto, et al⁽³⁵⁾ also evaluated the eosinophilic levels present in the nasal lavage, the peak inspiratory nasal flux, olfactometry and the necessity of adjuvant therapies during treatment. None of the analyzed variables displayed significant differences, even though there was a tendency for the intake of fewer antibiotic cycles, in treated patients.

Penn, et al⁽³⁴⁾ evaluated the total IgE serum levels: the average levels of total serum IgE were superior after the treatment cycle. This phenomenon is explained by the fact that the IgE-omalizumab complexes are excreted slower than free serum IgE⁽³⁷⁾.

Vennera, et al⁽³⁶⁾, studied the need of intranasal corticoid use before and after omalizumab treatment. They showed a significant reduction in the corticoids' needs after the therapeutic cycle with omalizumab (95% vs. 42%, p=0,002).

Discussion

Even though the pathophysiology CRSwNP remains, at least partially, obscure, there is now evidence that eosinophils and IgE play a definitive role. Such evidence suggests a pathophysiological mechanism similar to bronchial asthma. This observation is enforced by the important epidemiological association between these two nosological entities. Besides the significant effect it has in patients' quality of life and the social economic impact⁽³⁸⁾, there are some phenotypes of both diseases that are difficult to control using standard therapies.

In treatment of moderate-to-severe allergic asthma, omalizumab has a well-established role. However, its role in CRSwNP treatment is yet to be defined.

Evaluation of the variables analyzed in the studies included showed that nasal polyps endoscopic score results were not unanimous. Even though three of the articles showed significant improvements when comparing the pre and post treatment endoscopic scores, there was one⁽³⁵⁾ that did not mention any specific benefit. However, the study with the largest number of patients included⁽³³⁾, showed significant improvements, not only when comparing the omalizumab group pre and post treatment results, but also when results between the omalizumab and placebo groups were compared. If to these results we add the evidence from the other two studies^(34,36), it can be concluded that the omalizumab treatment has a positive role in nasal polyps' volume reduction. This observation is nevertheless limited by diverse staging criteria used in the different studies.

Another analyzed variable in this revision was the CRS with polyps' CT staging (sinus inflammation marker). Omalizumab's treated groups showed improvement in all studies^(33,34,35), even though Penn, et al⁽³⁴⁾ did not achieve statistical significance. This suggests that omalizumab is effective, at least short-term, in sinonasal inflammation. Once again, these conclusions are partially limited by the fact that different staging protocols were used.

The analysis of studies where QoL evaluation tools were used^(33,35) seemed to show some benefit from treatment with omalizumab, mainly in the specific CRS with polyps' symptoms analysis.

One of the main limitations of both RCT is a reduced follow-up time (5 and 6 months). Given that CRS with polyps has a late relapse potential, this fact limits the

conclusions on omalizumab's long-term effectiveness in the treatment of CRS with polyps. Another constrain refers to Gevaert, et al⁽³³⁾ study where patients did not continue usual chronic medical treatment. This limits, at least partially, the capacity to prove the superiority of omalizumab.

An issue that has been raising some concerns about omalizumab is its safety. Apart from flu (which is relatively frequent), there are two potential major side effects: anaphylaxis and malignant neoplasms. Post omalizumab treatment anaphylaxis is a rare, but potentially fatal side effect⁽³⁹⁾. However, it is recommended that patients remain monitored for hours after the treatment and this has significantly reduced occurrences outside of hospital environment⁽³⁹⁾. On the subject of neoplastic risk, a meta-analysis⁽⁴⁰⁾ did not find any association between omalizumab treatment and an augmented malignant neoplastic risk, suggesting that this link is highly unlikely.

There are already, to the extent of our knowledge, two classic revisions^(41,42) on the theme discussed above. Yet, none of them actually thoroughly analyzes all of the articles included here or used this type of methodology.

Conclusion

At the moment, evidence on omalizumab's effectiveness in CRSwNP treatment is low. However, the available literature indicates that it could be an effective therapeutic alternative. In particularly aggressive forms of the disease, where one expects early relapses, either after medical or surgical treatment, omalizumab may be a valid therapeutical alternative. This is true especially for patients with concomitant asthma.

More RCT's with bigger sample sizes, extended follow-up time and study design that allows enrolled patients to maintain chronic medical therapy are needed to unequivocally validate omalizumab's proper role in CRSwNP treatment.

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