Living FRIendly Summaries of the Body of Evidence using Epistemonikos (FRISBEE)

Omalizumab for chronic rhinosinusitis

Rocío Brañes[a,b], Andrés Rosenbaum[b,c], Claudio Callejas[c], Matías Winter[b,c]

[a] Facultad de Medicina, Pontificia Universidad Católica de Chile, Santiago, Chile
[b] Proyecto Epistemonikos, Santiago, Chile
[c] Departamento de Otorrinolaringología, Facultad de Medicina, Pontificia Universidad Católica de Chile, Santiago, Chile

***Corresponding author** mwinterd@gmail.com

Citation Brañes R, Rosenbaum A, Callejas C, Winter M. Omalizumab for chronic rhinosinusitis. *Medwave* 2018;18(7):e7346

Doi 10.5867/medwave.2018.07.7346

Submission date 27/8/2018
Acceptance date 15/11/2018
Publication date 23/11/2018

Origin This article is a product of the Evidence Synthesis Project of Epistemonikos Fundation, in collaboration with Medwave for its publication

Type of review Non-blinded peer review by members of the methodological team of Epistemonikos Evidence Synthesis Project

Potential conflicts of interest The authors do not have relevant interests to declare.

Key words Chronic rhinosinusitis, omalizumab, Epistemonikos, GRADE

Abstract

Introduction

Chronic rhinosinusitis is a high prevalence chronic inflammatory disease that involves nasal mucosa and paranasal sinuses. Immunoglobulin E is an inflammatory mediator that plays an etiopathogenic role in this condition, so omalizumab, an anti-immunoglobulin E monoclonal antibody, might be a therapeutic alternative.

Methods

We searched in Epistemonikos, the largest database of systematic reviews in health, which is maintained by screening multiple information sources, including MEDLINE, EMBASE, Cochrane, among others. We extracted data from the systematic reviews, reanalyzed data of primary studies, conducted a meta-analysis and generated a summary of findings table using the GRADE approach.

Results and conclusions

We identified five systematic reviews that included five primary studies overall, of which two correspond to randomized trials. We concluded it is not clear whether omalizumab leads to an improvement in the nasal polyps scale, quality of life, general well-being or nasal symptoms in patients with chronic rhinosinusitis, because the certainty of the evidence is very low. On the other hand, omalizumab is probably associated with frequent adverse effects.

Problem

Chronic rhinosinusitis is an inflammatory disease of the mucosa of the nasal cavity and paranasal sinuses lasting longer than 12 weeks. It is a common disease that could affect more than 15% of the total population in the United States[1], which is why it is an important health problem that affects quality of life. Although there are therapeutic alternatives, a group of patients remains symptomatic. It has been suggested that this may be due to most treatments focusing on relief of symptoms and reduction of inflammation, rather than in the cause. Current research has changed the approach to target barrier responses and states of chronic inflammation[2].

Omalizumab is a humanized monoclonal antibody that selectively binds to the crystallizable fragment (Fc) region of immunoglobulin E (IgE) by reducing free immunoglobulin E, which produces an anti-inflammatory effect and apoptosis of eosinophils. However, it is not clear to what extent this is translated into a clinical effect. The objective of the arthrodesis to arthroplasty conversion is to restore the range of movement in the joint, leading to an improvement in the functionality of the patient. However, it is not a procedure that is performed frequently, since it is technically demanding and has a high rate of complications. It is currently unclear what is the role of the conversion of arthrodesis to total knee arthroplasty.

Key messages

- It is not clear whether omalizumab leads to an improvement in the Nasal Polyps Score, quality of life, general well-being or nasal symptoms in chronic rhinosinusitis, because the certainty of the evidence is very low.
- Omalizumab is probably associated with frequent adverse effects.

About the body of evidence for this question

What is the evidence. See evidence matrix in Epistemonikos later	We found five systematic reviews[3-8] that included five primary studies[9-13] of which two correspond to randomized controlled trials[9,12]. This table and the summary in general are based on the two randomized trials[9,12], given the observational studies did not increase the certainty of the existing evidence or provide relevant additional information.
What types of patients were included*	Both trials included patients older than 18 years [9,12]. One trial evaluated patients suffering from chronic rhinosinusitis with nasal polyps and asthma for more than 2 years [12], and the other trial evaluated patients after sinus surgery[9].
What types of interventions were included*	All trials used omalizumab as an intervention. One trial administered omalizumab 150-375 mg every 2 weeks[12] and another 0,016 mg/kg once a month[9]. Both trials compared the intervention against placebo.
What types of outcomes were measured	The trials evaluated multiple outcomes, which were grouped by the systematic reviews as follows: • Nasal Polyp Scale (Nasal Polyp Score - NPS) • Nasal symptoms- Quality of life and general well-being • Adverse effects: such as headache, nasal obstruction, shortness of breath, allergies, common cold, gastroenteritis, otitis media, shoulder of pain and left ulnar hypoaesthesia. The average follow-up was 12.9 months, with a range between 5 and 28 months.

* The information about primary studies is extracted from the systematic reviews identified, unless otherwise specified.

Methods

To answer the question, we used Epistemonikos, the largest database of systematic reviews in health, which is maintained by screening multiple information sources, including MEDLINE, EMBASE, Cochrane, among others, to identify systematic reviews and their included primary studies. We extracted data from the identified reviews and reanalyzed data from primary studies included in those reviews. With this information, we generated a structured summary denominated FRISBEE (Friendly Summary of Body of Evidence using Epistemonikos) using a pre-established format, which includes key messages, a summary of the body of evidence (presented as an evidence matrix in Epistemonikos), meta-analysis of the total of studies when it is possible, a summary of findings table following the GRADE approach and a table of other considerations for decision-making.

Summary of Findings

The information on the effects of omalizumab in chronic rhinosinusitis is based on two randomized trials that included 38 patients[9,12].

Both trials reported the effect on the Nasal Polyp Score (31 patients), changes in quality of life (38 patients) and nasal symptoms (38 patients)[9,12]. Only one trial reported adverse effects (24 patients)[12].

The summary of findings is as follows:

- It is not clear whether omalizumab leads to an improvement in the Nasal Polyps Score in chronic rhinosinusitis because the certainty of the evidence is very low.
- It is not clear whether omalizumab leads to an improvement in quality of life and general well-being because the certainty of the evidence is very low.
- It is not clear whether omalizumab leads to an improvement in nasal symptoms (nasal obstruction, loss of sense of smell and presence of rhinorrhea) because the certainty of the evidence is very low.
- Omalizumab probably has adverse effects in patients with chronic rhinosinusitis. The certainty of the evidence is moderate.

Omalizumab for chronic rhinosinusitis

Patients Chronic rhinosinusitis
Intervention Omalizumab
Comparison Placebo

Outcome	Absolute effect*		Relative effect (95% CI)	Certainty of evidence (GRADE)
	WITHOUT omalizumab	**WITH omalizumab**		
	Difference: patients per 1000			
Nasal polyps scale **	MD 1.1 points better (4.08 better to 1.89 worse)		--	⨁◯◯◯[1,2,3] Very low
Quality of life and general well-being	Omalizumab improved the score on symptom scales RSOM-31 and SNOT-20 [9],[12].			⨁◯◯◯[2,4] Very low
Nasal symptoms	Omalizumab improved nasal symptoms, such as nasal obstruction, anterior rhinorrhea and smell alterations [9],[12].			⨁◯◯◯[2,4] Very low
Adverse effects	95.7% of the participants reported at least one adverse event, most of them mild. The common cold was the most frequent [12].			⨁⨁⨁◯[2,4] Moderate

Margin of error: 95% confidence interval (CI).
MD: Mean difference.
GRADE: Evidence grades of the GRADE Working Group (see later).

*The risk **WITHOUT omalizumab** is based on the risk in the control group of the trials. The risk **WITH omalizumab** (and its margin of error) is calculated from relative effect (and its margin of error).
** *Nasal Polyp Score:* The polyp scoring system used to evaluate the size of the polyp in each nostril by nasal endoscopy with a Likert scale that ranges from a score of 0= "without polyps", score 2= "polyps that are found below the lower limit of the middle turbinate ", score 3=" large polyps that reach the lower edge of the inferior turbinate or medial polyps to the middle shell", up to a maximum of 4=" Large polyps that cause complete obstruction of the lower nasal cavity. "

[1] The certainty of evidence was downgraded one level due to inconsistency (I2 = 73%).
[2] The certainty of evidence was downgraded one level for risk of bias because the randomization sequence generation and concealment were not clear, and there was not blinding. The certainty on adverse effects was not decreased by this factor, since in the absence of bias the conclusion would be reinforced.
[3] The certainty of evidence was downgraded one level for imprecision because the confidence interval includes the possibility that there is an effect of minimal clinical relevance, and each end of this interval would lead to different decisions.
[4] The certainty of evidence was downgraded one level for imprecision due to the small sample size of the trials.

Follow the link to access the interactive version of this table (Interactive Summary of Findings – iSoF)

About the certainty of the evidence (GRADE)*

⊕⊕⊕⊕
High: This research provides a very good indication of the likely effect. The likelihood that the effect will be substantially different† is low.

⊕⊕⊕◯
Moderate: This research provides a good indication of the likely effect. The likelihood that the effect will be substantially different† is moderate.

⊕⊕◯◯
Low: This research provides some indication of the likely effect. However, the likelihood that it will be substantially different† is high.

⊕◯◯◯
Very low: This research does not provide a reliable indication of the likely effect. The likelihood that the effect will be substantially different† is very high.

* This concept is also called 'quality of the evidence' or 'confidence in effect estimates'.

† Substantially different = a large enough difference that it might affect a decision

Other considerations for decision-making

To whom this evidence does and does not apply

The conclusions of this summary apply to adults patients with chronic rhinosinusitis.

Due to the limitations of the identified evidence, it is not possible to draw conclusions about whether there is a subgroup of patients that especially benefits from the intervention.

About the outcomes included in this summary

Among the outcomes evaluated in the table are those considered critical for decision making, according to the opinion of the authors of this summary.

It was decided to focus on the changes in the nasal polyps scale, which is an outcome widely used in the clinic, and for which the trials provided the necessary information to conduct a meta-analysis.

Although both trials included changes in computed tomography of paranasal cavities within their outcomes, it was decided not to include them in the summary of findings table because it is a surrogate outcome.

Balance between benefits and risks, and certainty of the evidence

It is not possible to make an adequate balance between the risks and benefits of omalizumab in patients with chronic rhinosinusitis, due to the uncertainty about the benefits.

On the other hand, although the trials have a small sample size, the evidence is sufficient to conclude that the adverse effects are probably frequent.

Resource considerations

Omalizumab is a high-cost intervention, so it is particularly important for decision making to have accurate information about the benefits. Given the uncertainty associated with the benefits, it is not possible to make an adequate estimation of the cost-benefit.

What would patients and their doctors think about this intervention

Faced with the evidence presented in this summary, most clinicians and patients should lean against the use of omalizumab as the first therapeutic line in chronic rhinosinusitis, mainly due to the uncertainty about its benefit, its cost and the frequency of adverse effects.

However, in refractory cases or with comorbidities, it is likely that some people may be inclined to use it, especially if there are no resource constraints.

Differences between this summary and other sources

This summary presents concordant conclusions with those of the six systematic reviews identified[3-8].

The conclusions of this summary agree with the European Consensus on Rhinosinusitis and Nasal Polyps 2012[2].

Could this evidence change in the future?

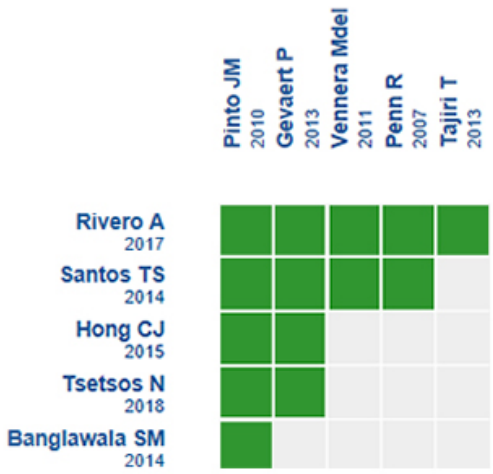
It is very likely that future evidence will change the conclusions of this summary, due to the uncertainty about the benefits.

We identified three ongoing trials in the International Clinical Trials Registry Platform of the World Health Organization on the use of Omalizumab in chronic rhinosinusitis with polyps[14,15,16].

No systematic reviews in progress were found in the PROSPERO database (International Prospective Register of Systematic Reviews).

How we conducted this summary

Using automated and collaborative means, we compiled all the relevant evidence for the question of interest and we present it as a matrix of evidence.



An evidence matrix is a table that compares systematic reviews that answer the same question.
Rows represent systematic reviews, and columns show primary studies.
The boxes in green correspond to studies included in the respective revisions.
The system automatically detects new systematic reviews including any of the primary studies in the matrix, which will be added if they actually answer the same question.

Follow the link to access the **interactive version:** Omalizumab for chronic rhinosinusitis.

Notes

The upper portion of the matrix of evidence will display a warning of "new evidence" if new systematic reviews are published after the publication of this summary. Even though the project considers the periodical update of these summaries, users are invited to comment in *Medwave* or to contact the authors through email if they find new evidence and the summary should be updated earlier.

After creating an account in Epistemonikos, users will be able to save the matrixes and to receive automated notifications any time new evidence potentially relevant for the question appears.

This article is part of the Epistemonikos Evidence Synthesis project. It is elaborated with a pre-established methodology, following rigorous methodological standards and internal peer review process. Each of these articles corresponds to a summary, denominated FRISBEE (Friendly Summary of Body of Evidence using Epistemonikos), whose main objective is to synthesize the body of evidence for a specific question, with a friendly format to clinical professionals. Its main resources are based on the evidence matrix of Epistemonikos and analysis of results using GRADE methodology. Further details of the methods for developing this FRISBEE are described here (http://dx.doi.org/10.5867/medwave.2014.06.5997)

Epistemonikos foundation is a non-for-profit organization aiming to bring information closer to health decision-makers with technology. Its main development is Epistemonikos database

www.epistemonikos.org.

Referencias

1. Collins JG, Blackwell DL, Tonthat L, Shashy RG, Moore EJ, Weaver A, et al. Prevalence of selected chronic conditions: United States, 1990-1992 Summary health statistics for the U.S. population: National Health Interview Survey, 1997 Prevalence of the chronic sinusitis diagnosis in Olmsted County, Minnesota The role of nasal endoscopy in outpatient management. Vital Health Stat 10. 1997;130(194):1-89.
2. Fokkens WJ, Lund VJ, Mullol J, Bachert C, Alobid I, Baroody F, Cohen N, Cervin A, Douglas R, Gevaert P, Georgalas C, Goossens H, Harvey R, Hellings P, Hopkins C, Jones N, Joos G, Kalogjera L, Kern B, Kowalski M, Price D, Riechelmann H, Schlosser R, Senior B, Thomas M, Toskala E, Voegels R, Wang de Y, Wormald PJ. EPOS 2012: European position paper on rhinosinusitis and nasal polyps 2012. A summary for otorhinolaryngologists. Rhinology. 2012 Mar;50(1):1-12. | CrossRef | PubMed |
3. Hong CJ, Tsang AC, Quinn JG, Bonaparte JP, Stevens A, Kilty SJ. Anti-IgE monoclonal antibody therapy for the treatment of chronic rhinosinusitis: a systematic review. Syst Rev. 2015 Nov 18;4:166. | CrossRef | PubMed | PMC |
4. Santos TS, Certal VF, Gonçalves P, Carvalho C. Effectiveness of omalizumab in the treatment of chronic rhinosinusitis with nasal polyps: systematic review. European Scientific Journal, ESJ. 2014;10(10).
5. Banglawala SM, Oyer SL, Lohia S, Psaltis AJ, Soler ZM, Schlosser RJ. Olfactory outcomes in chronic rhinosinusitis with nasal polyposis after medical treatments: a systematic review and meta-analysis. Int Forum Allergy Rhinol. 2014 Dec;4(12):986-94. | CrossRef | PubMed |
6. Rivero A, Liang J. Anti-IgE and Anti-IL5 Biologic Therapy in the Treatment of Nasal Polyposis: A Systematic Review and Meta-analysis. The Annals of otology, rhinology, and laryngology. 2017;126(11):3489417731782.
7. Rix I, Håkansson K, Larsen CG, Frendø M, von Buchwald C. Management of chronic rhinosinusitis with nasal polyps and coexisting asthma: A systematic review. American journal of rhinology & allergy. 2015;29(3):193-201.
8. Tsetsos N, Goudakos JK, Daskalakis D, Konstantinidis I, Markou K. Monoclonal antibodies for the treatment of chronic rhinosinusitis with nasal polyposis: a systematic review. Rhinology. 2018;56(1):11-21.
9. Pinto JM, Mehta N, DiTineo M, Wang J, Baroody FM, Naclerio RM. A randomized, double-blind, placebo-controlled trial of anti-IgE for chronic rhinosinusitis. Rhinology. 2010;48(3):318-24.
10. Vennera Mdel C, Picado C, Mullol J, Alobid I, Bernal-Sprekelsen M. Efficacy of omalizumab in the treatment of nasal polyps. Thorax. 2011;66(9):824-5.
11. Penn R, Mikula S. The role of anti-IgE immunoglobulin therapy in nasal polyposis: a pilot study. Am J Rhinol. 2007;21(4):428-32.
12. Gevaert P, Calus L, Van Zele T, Blomme K, De Ruyck N, Bauters W, Hellings P, Brusselle G, De Bacquer D, van Cauwenberge P, Bachert

C. Omalizumab is effective in allergic and nonallergic patients with nasal polyps and asthma. The Journal of allergy and clinical immunology. 2013;131(1):110-6.e1.
13. Tajiri T, Matsumoto H, Hiraumi H, Ikeda H, Morita K, Izuhara K, Ono J, Ohta S, Ito I, Oguma T, Nakaji H, Inoue H, Iwata T, Nagasaki T, Kanemitsu Y, Ito J, Niimi A, Mishima M. Efficacy of omalizumab in eosinophilic chronic rhinosinusitis patients with asthma. Annals of allergy, asthma & immunology : official publication of the American College of Allergy, Asthma, & Immunology. 2013;110(5):387-8.
14. Hoffmann-La Roche. An Extension Study of Omalizumab in Participants With Chronic Rhinosinusitis With Nasal Polyps. clinicaltrials.gov. 2018.
15. Hoffmann-La Roche. A Clinical Trial of Omalizumab in Participants With Chronic Rhinosinusitis With Nasal Polyps. clinicaltrials.gov. 2017.
16. Medical University of Vienna. Effect of Omalizumab in patients with Aspirin intolerance, nasal polyposis and allergic asthma. EUCTR2017-003119-21-AT.

Correspondencia a
Centro Evidencia UC
Pontificia Universidad Católica de Chile
Diagonal Paraguay 476
Santiago
Chile