

Abreviaturas: Interleukin 5, chronic rhinosinusitis, nasal polyps, Epistemonikos, GRADE.

Abstract

INTRODUCTION

Chronic rhinosinusitis is the inflammation of sinonasal mucosa lasting longer than 12 weeks. Two clinical forms are distinguished: chronic rhinosinusitis with polyps and without polyps. Patients with chronic rhinosinusitis with polyps exhibit high levels of interleukin 5, which promotes differentiation and survival of eosinophils. So, minimizing their circulation has been proposed as a new treatment strategy. However, there is no clarity regarding its real effectiveness.

METHODS

To answer this 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. 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 three systematic reviews included three primary studies overall, all corresponding to randomized trials. We concluded inhibitors of interleukin 5 might decrease nasal polyps score. Although they might be associated with adverse effects, these would be infrequent and of low severity. However, the certainty of the evidence is low.

Problem

Chronic rhinosinusitis is a chronic inflammatory disease of the sinonasal mucosa lasting longer than 12 weeks. It is estimated that 11.9% and 10.9% of the general population of the United States and Europe, respectively, have chronic rhinosinusitis

[1] (<https://www.medwave.cl/webactivo/editor.cgi?id=7300&num=1&web=1#>),

[2] (<https://www.medwave.cl/webactivo/editor.cgi?id=7300&num=1&web=1#>) whose symptoms significantly reduce physical and psychological well-being, affecting quality of life.

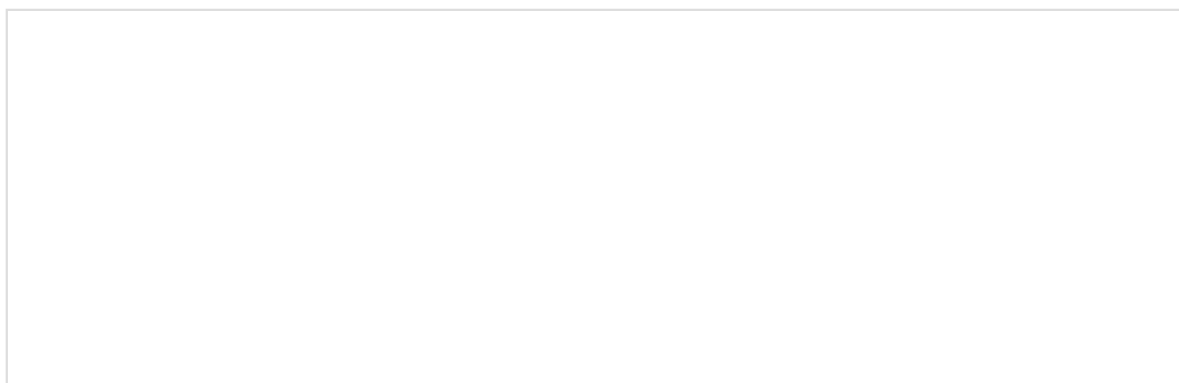
Medical treatment traditionally includes nasal washes and topical corticosteroids as maintenance therapy; systemic corticosteroids and antibiotics for exacerbations, and functional endoscopic surgery of paranasal cavities when medical and pharmacological treatment is not effective. However, there are many patients who do not respond or respond partially to treatment. One potential explanation is it focus on the relief of symptoms and reduction of inflammation rather than the cause of the disease. Interleukin 5 is a key mediator of chemotaxis, differentiation, activation and survival of the eosinophils

[3] (<https://www.medwave.cl/webactivo/editor.cgi?id=7300&num=1&web=1#>). Inhibiting this pathway would stop the release of toxic products that lead to more and lasting inflammation and formation of polyps in patients with chronic rhinosinusitis

[4] (<https://www.medwave.cl/webactivo/editor.cgi?id=7300&num=1&web=1#>). However, it is unclear what are the clinical effects of biological drugs that inhibit circulating interleukin 5, such as mepolizumab or reslizumab.

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 section of other considerations for decision-making.



Key messages

Inhibitors of interleukin 5 might decrease nasal polyps in patients with chronic rhinosinusitis refractory to medical and surgical treatment, but the certainty of the evidence is low.

Inhibitors of interleukin 5 might be associated to adverse effects of low frequency and severity, but the certainty of the evidence is low.

About the body of evidence for this question

What is the evidence. See evidence matrix in Epistemonikos later	We found three systematic reviews [5], [6], [7] that included three primary studies [8], [9], [10], all of which were randomized trials.
What types of patients were included*	All trials [8], [9], [10] included patients older than 18 years. Two trials [9], [10] included patients with a history of chronic rhinosinusitis and nasal polyps (grade 3 or 4) with failure to standard medical therapy or patients with recurrent nasal polyps after surgery (grade 1-4). One trial included patients with severe recurrent bilateral nasal polyposis who required surgery after failure of standard corticosteroid therapy [8].

What types of interventions were included*	All trials used interleukin 5 inhibitors: one trial [9] used reslizumab and two trials [8], [10] mepolizumab. Reslizumab was used in doses of 3 mg/kg and 1 mg/kg in a single dose. Mepolizumab was administered in two doses of 750 mg IV separated by 28 days in one trial [10] and in six doses of 750 mg IV separated by 4 weeks in the other [8]. The three trials compared the intervention against placebo [8], [9], [10].
What types of outcomes were measured	The trials evaluated multiple outcomes, which were grouped by the systematic reviews as follows: Nasal Polyp Scale Quality of life (SNOT-22) SymptomsPNIF (Peak nasal inspiratory flow) Adverse effects The average follow-up was 36 weeks, with a range between 25 and 48 weeks.

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

Summary of findings

The information on the effects of interleukin 5 inhibitors is based on three randomized trials

[8], [9], [10] that included 159 patients.

Two trials [9], [10] measured the Nasal Polyp Score and symptoms through questions about specific symptoms, such as nasal obstruction, loss of sense of smell and presence of rhinorrhea (54 patients). Two trials [8], [10] reported Peak nasal inspiratory flow and adverse effects (135 patients). Only one trial [8] evaluated quality of life using the SNOT-22 specific indicator (105 patients).

The summary of findings is as follows:

Inhibitors of interleukin 5 might decrease the score of nasal polyps, but the certainty of the evidence is low.

Inhibitors of interleukin 5 might not have an impact on quality of life measured in SNOT, but the certainty of the evidence is low.

It is not clear whether interleukin 5 inhibitors reduce symptoms (nasal obstruction, loss of sense of smell and presence of rhinorrhea) because the certainty of the evidence is very low.

Inhibitors of interleukin 5 might improve PNIF, but the certainty of the evidence is low.

Inhibitors of interleukin 5 might be associated to adverse effects of low frequency and severity, but the certainty of the evidence is low.

IL-5 inhibitors for chronic rhinosinusitis with polyps				
Patients	Chronic rhinosinusitis with polyps			
Intervention	Interleukin 5 (IL-5) inhibitors			
Comparison	Placebo			
Outcome	Absolute effect*		Relative effect (95% CI)	Certainty of evidence (GRADE)
	WITHOUT IL-5 inhibitor	WITH IL-5 inhibitor		
	Difference: patients per 1000			
Nasal Polyp Score **	SMD*: 0.66 less (Margin of error: 0.08 to 1.24 less)		--	⊕⊕○○ ^{1,2} Low
Quality of life (SNOT 22- Sino-nasal Outcome Test) ***	The score was 51.05 in the intervention group and 49.5 in the control group in one trial. The difference was reported as statistically significant.			⊕⊕○○ ³ Low
Symptoms****	Two trials [9], [10] indicated there were differences in symptoms measured with non-standardized scales.			⊕○○○ ^{1,4} Very Low
PNIF (Peak Nasal Inspiratory Flow)	One trial [10] reported there were non-significant differences. In contrast, another trial [8] estimated there were statistically significant differences.			⊕⊕○○ ^{1,5} Low
Adverse effects	In one trial [10] there were 21/3 adverse effects in the intervention/control group. In another trial [8] there were 40/42 adverse effects in intervention/control. The most common adverse effects were cold and headache			⊕⊕○○ ^{1,5} Low
Margin of error: 95% confidence interval (CI). SMD: Standardized mean difference GRADE: Evidence grades of the GRADE Working Group (see later).				
* The standardized difference in means is used when the outcome has been measured at different scales and is difficult to interpret clinically. A general rule is that values less than 0.2 are of little clinical relevance, values of 0.5 of moderate relevance and 0.8 of important clinical relevance. ** Nasal Polyp Score: The polyp scoring system used to evaluate the size of the polyp in each nostril by nasal endoscopy, with a score of 0 = "without polyps" up to a maximum of 4 = "large polyps causing complete obstruction of the lower nasal cavity. " *** Sino- Nasal Outcome test 22: Specific indicator of the impact on quality of life in patients with nasosinus pathology. It is a questionnaire with 22 symptoms or social / emotional consequences associated with chronic rhinosinusitis, evaluating each item with a Likert scale of 0 to 5. The value of the score ranges from 0 to 110. **** Reported symptoms: nasal obstruction, loss of sense of smell and presence of rhinorrhea. 1 A level of certainty of evidence was reduced due to risk of bias mainly because the sequence of allocation, concealment of it, or whether it was blind was unclear. 2 One level of certainty of evidence was reduced due to imprecision since each end of the confidence interval entails a different decision. 3 Two levels of certainty of evidence were reduced due to imprecision, since the estimate is based on a single, small study. 4 Two levels of certainty of evidence were reduced due to imprecision. 5 One level of certainty of evidence was decreased for inconsistency, since the conclusions of the trials are discrepant.				

Follow the link to access the interactive version of this table (Interactive Summary of Findings – iSoF
(<https://isof.epistemonikos.org/#/finding/5bc8653de3089d07c9b556bf>)

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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 diagnosed with chronic rhinosinusitis with nasal polyps, refractory to medical and surgical treatment.

Only one trial [10] mentioned that the diagnosis of chronic rhinosinusitis was based on the European position paper on rhinosinusitis and NPs 2007 [11].

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.

There could be effects on other outcomes, such as change in the tomographic profile according to the Lund-Mackay classification, but they were not reported in the systematic reviews identified.

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 anti-interleukin 5 therapy in patients with chronic rhinosinusitis with polyps refractory to medical and surgical treatment, due to the uncertainty about the benefits.

On the other hand, the trials evaluating the efficacy of anti-interleukin 5, reported few and mild adverse effects, the most frequent being headache and common cold. However, the certainty of the evidence is low.

Resource considerations

Biological therapies, such as interleukin 5 inhibitors, are generally high-cost medications, compared to other alternatives commonly used in patients with chronic rhinosinusitis with polyps. In addition, given the uncertainty associated with the benefits, especially on the most important outcomes, such as improvement in symptoms and quality of life, it is not possible to estimate an adequate cost/benefit.

What would patients and their doctors think about this intervention

Most clinicians should lean against the use of this intervention, as it is an alternative of uncertain benefit and relatively high cost.

Considering the impact on quality of life in patients not responding to multiple treatments, some people may be inclined to try this unproven therapy, particularly in scenarios where there are no resource constraints.

Differences between this summary and other sources

The conclusions of this summary agree with the systematic reviews identified.

The European Consensus on rhinosinusitis and nasal polyps 2012 [12] recommends anti-interleukin 5 therapy for adults with chronic rhinosinusitis with operated nasal polyps, and adults with chronic rhinosinusitis with non-operated nasal polyps.

Could this evidence change in the future?

The likelihood of future research changing the conclusions of this summary is high, due to the existing uncertainty provided by the existing evidence in relation to the change in the Nasal Polyps Score, quality of life and nasal symptoms.

We did not identify ongoing trials on this topic in the International Clinical Trials Registry Platform of the World Health Organization.

No ongoing systematic reviews 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.

	Bachert C 2017	Gevaert P 2006	Gevaert P 2011
Tsetsos N 2018			
Rudmik L 2015			
Rivero A 2017			

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**:

Anti IL5 for chronic rhinosinusitis with polyps

(<http://www.epistemonikos.org/en/matrixes/5af614596ec0d673adf4cca6>)

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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 (<http://www.epistemonikos.org/>)).

Potential conflicts of interest

The authors do not have relevant interests to declare.



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