

## PROGNOSTIC VALUE OF IL-5 IN SINUS LAVAGE IN PATIENTS WITH CHRONIC MAXILLARY SINUSITIS

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**SUMMARY** – The aim of the study was to evaluate subjective outcomes in patients with chronic rhinosinusitis after steroid/antibiotic endonasal treatment and to test the hypothesis that pretreatment levels of the cytokine interleukin-5 in sinus fluid could predict response to endonasal steroid/antibiotic treatment. Twenty-four patients with symptoms of chronic rhinosinusitis were recruited for the study. Inclusion criteria were sinusitis symptoms persisting for more than three months and maxillary sinus mucosa thickening by >6 mm, considered as maxillary sinusitis. Patients with asthma, polyposis, recent infection, systemic steroid therapy or previous sinus surgery were excluded. Patients were treated endonasally with 2 mg dexamethasone and 40 mg gentamicin *per* maxillary sinus daily for 5 days. Patients rated nasal/chronic rhinosinusitis disease-specific symptoms and completed a self-administered questionnaire concerning sinusitis symptoms at inclusion and after 30 days. Sinus lavage collected at inclusion was analyzed for interleukin-5 concentration. Endonasal treatment led to improvement with symptom alleviation in ten (52.6%) patients (responders), whereas unchanged or worsened condition was recorded in nine (47.4%) patients (nonresponders). Significant improvement was noted for overall sinusitis symptom score ( $p=0.02$ ), and for obstruction, postnasal drip, headache, sneezing and cough ( $p<0.05$ ) in the study group as a whole. There was a positive correlation of baseline interleukin-5 level in sinus lavage with the improvement rate of overall sinusitis symptom score ( $p<0.01$ ) and improvement rate of nasal secretion score ( $p<0.01$ ). Results indicated the increased interleukin-5 levels in sinus fluid to predict good response to endonasal steroid/antibiotic treatment.

**Key words:** *Maxillary sinusitis – drug therapy; Chronic disease; Sinusitis – complications; Cytokines – metabolism*

### Introduction

Chronic rhinosinusitis (CRS) is one of the most common chronic disorders, with a significant impact on the health-related quality of life (HRQL)<sup>1</sup>. It is defined by its subjective signs, i.e. severity and duration of characteristic symptoms of postnasal drip, nasal obstruction and discharge, facial pressure or pain, headache, cough and olfactory disorders persisting for more than 12 weeks. The severity of objective findings used for diagnosis and staging of CRS (x-ray, sinus computed tomography (CT) scans, bacteriology, inflammatory mediators) do not correlate

with the subjective symptom scores, but some of objective signs have been reported to be valuable predictors of poor longterm outcome following conservative or surgical treatment<sup>2</sup>. Evaluation of different conservative CRS treatment modalities in randomized controlled trials indicated a limited value of nonsurgical treatment for acceptable longterm outcomes. Medications usually recommended for CRS management are a combination of longacting antibiotics, topical nasal steroids, hypertonic or saline nasal douches, and short-term nasal decongestants. A wide range of surgical procedures have been used to treat this condition, from simple sinus puncture to functional endoscopic sinus surgery. In some studies, up to 50% of allergic patients with CRS do not improve after surgery<sup>2,3</sup>. Maxillary antrostomy through the inferior meatus is a minor but common otolaryngologic procedure, usually followed by

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irrigation and topical application of the drug into the maxillary sinus, performed under local anesthesia. Simple sinus irrigation combined with oral antibiotics prevented sinus surgery in more than half of CRS patients<sup>4</sup>.

Allergic reaction in the airways may induce dysregulated immune/inflammatory response also in the sinus mucosa and lead to an increased density of certain inflammatory cells, i.e. T and B lymphocytes, activated eosinophils and IgE positive mast cells, although such changes have also been noted in patients with noninfective nonallergic rhinitis. Cellular recruitment and activation have been largely attributed to the upregulation of T-helper cell type 2 cytokines (i.e. interleukin-4 (IL-4), IL-5, IL-13, and granulocyte-macrophage colony-stimulating factor). IL-5 is involved in eosinophil differentiation, activation and delayed apoptosis, enhancing their survival<sup>5</sup>. Its activity is down-regulated by topical/systemic steroid treatment.

Accurate assessment of post-therapeutic subjective outcome in CRS patients requires collection of valid and reliable data, as the disease is defined by subjective signs<sup>6</sup>. An important outcome measure in such patients is HRQL score, as it demonstrates the efficacy of interventions<sup>7</sup>. Topical steroid treatment as well as sinus surgery modifies patient symptom profile and HRQL<sup>8,9</sup>. Evaluation of subjective symptom scores by HRQL questionnaire in CRS patients should be more uniform for proper meta-analyses on evaluating studies of different treatment modalities<sup>10</sup>.

The aim of this study was to evaluate subjective outcomes in patients with CRS after steroid/antibiotic endosinusal treatment, and to correlate these subjective outcomes with pretreatment levels of IL-5 (Th-2 cytokine) in sinus fluid, testing the hypothesis that the levels of this cytokine could predict the response to endosinusal medication (presumably steroid) used in this trial.

## Patients and Methods

Twenty-four patients (13 female and 11 male), mean age  $42 \pm 16.9$  years, with symptoms of CRS were recruited for the study. Eleven (45.8%) patients were categorized as allergic and 13 (54.2%) as nonallergic. All patients gave their informed consent and the study was approved by the Ethics Committee of Sestre milosrdnice University Hospital, Zagreb, Croatia. The patients were enrolled between February and June 2002. Inclusion criteria were sinusitis symptoms lasting for more than three months and maxillary sinus mucosal thickening by more than 6 mm (x-ray Waters' projection or ultrasound image), considered as maxillary sinusitis. Exclusion criteria were bronchial asthma,

nasal polyposis, recent upper respiratory infection, systemic steroid therapy, any systemic disease, or previous sinus surgery.

During the study, patients were treated with 2 mg dexamethasone and 40 mg gentamicin *per* maxillary sinus/day (according to the Croatian guidelines for the treatment of sinusitis sponsored by the Croatian Ministry of Health), applied through a polyethylene anastomosis tube inserted by antral sinuscopy through the inferior meatus in local anesthesia. Sinus lavage with 5 ccm of saline was taken prior to the first endosinusal treatment. During the 5-day treatment period, the patients did not receive any additional antibiotic or antiallergic treatment.

IL-5 was determined by radioimmunoassay (Pharmacia, Sweden).

Patients rated their nasal/CRS disease-specific symptoms and completed a self-administered questionnaire on major (obstruction, postnasal drip, headache, discharge, sneezing) and minor (facial swelling, cough, nasal itching, olfaction or taste disturbances) sinusitis symptoms before intervention and at one-month follow-up. Outcome was assessed in each patient by a questionnaire in which the patient rated the severity and frequency of different symptoms at a 0-3 scale. Sinusitis symptom scores are presented as a mean value of 10 symptom scores<sup>11</sup>. The rate of sinusitis symptom score improvement (symptomatic improvement rate) was calculated as difference between the posttreatment and pretreatment scores. The subjects were categorized into responders and nonresponders to endosinusal treatment by use of the symptomatic improvement rate. The subjects who declared a total score improvement rate of 1 or more at one month after the treatment were considered as responders.

## Statistics

Statistical analyses were performed with the Smirnov-Kolmogorov test, followed by Wilcoxon Signed Ranks test, for comparison of the sinusitis symptom scores. Comparison between responders and nonresponders was done by use of Student's unpaired t-test for IL-5, and by Mann-Whitney U test for sinusitis symptom scores. Correlations were calculated with Spearman rank correlation coefficient. All conclusions were based on a significance level of  $p < 0.05$ .

## Results

Out of 24 patients with symptoms of CRS recruited, five did not complete the study and were excluded, and 19 (79.2%) patients completed the study. The rate of

Table 1. Mean ( $\pm$ SD) baseline sinus lavage concentrations of interleukin-5 (pg/ml) in total patient sample and patient groups (responders/nonresponders and allergic/nonallergic); pretreatment (1) and post-treatment (2) sinusitis symptom scores

	Total (N=19)	Responders (n=10)	Nonresponders (n=9)	Allergic (n=9)	Nonallergic (n=10)
Interleukin-5	9.56 $\pm$ 7.1	16.28 $\pm$ 13.2*	7.3 $\pm$ 1.48*	10.51 $\pm$ 8.95	10.76 $\pm$ 9.68
Symptoms 1	2.4 $\pm$ 1.13*	2.76 $\pm$ 0.073	2.34 $\pm$ 1.29	3.15 $\pm$ 0.93	1.95 $\pm$ 1.083
Symptoms 2	1.81 $\pm$ 1.33*	1.4 $\pm$ 0.67	1.96 $\pm$ 1.5	2.29 $\pm$ 1.19	1.46 $\pm$ 1.37

\*p<0.01

improvement was calculated and patients were categorized as responders or nonresponders according to the severity of nasal symptoms before and one month after the treatment. Ten (52.6%) patients showed improvement and symptom alleviation after endonasal treatment (responders). Nine (47.4%) patients were unchanged or worsened (IR<1) after the treatment (nonresponders).

The results of baseline sinus lavage analyses for IL-5, and pretreatment and post-treatment sinusitis symptom scores for the study group as a whole (N=19) as well as for the responder/nonresponder and allergic/nonallergic subgroups are summarized in Table 1.

On day 30, significant improvement was recorded for overall sinusitis symptom score (p=0.02) and for obstruction, postnasal drip, headache, sneezing and cough (p<0.05) in the study group as a whole. Other symptoms such as nasal discharge, facial swelling, nasal itching, and olfaction or taste disturbances failed to show significant improvement at one-month follow-up. Difference in baseline IL-5 level in sinus lavage between the responders (16.28 $\pm$ 13.2) and nonresponders (7.3 $\pm$ 1.48) was significant (p=0.003). Difference in baseline IL-5 level in sinus lavage between allergic (10.51 $\pm$ 8.95) and nonallergic (10.76 $\pm$ 9.68) patients was not significant. There was no significant difference in the pretreatment and post-treatment sinusitis symptom scores between allergic and non-allergic patients.

Table 2 shows correlations between baseline IL-5 levels and rate of the sinusitis symptom score improvement. There was a positive correlation of baseline IL-5 level in sinus lavage with improvement rate of overall sinusitis symptom score (p<0.01) and improvement rate of nasal secretion score (p<0.05). There was a significant inverse correlation between baseline IL-5 level in sinus lavage and improvement rate of headache score (p<0.05).

The results indicated lower baseline IL-5 levels in sinus lavage to be associated with lower individual improvement rate of symptom scores.

## Discussion

This study was undertaken to evaluate the prognostic value of IL-5 level in pretreatment sinus lavage related to 5-day steroid/antibiotic endonasal treatment, in terms of reduction of subjective symptom scores in CRS patients. Studies of the prognostic value of pretreatment sinus CT scans, tissue eosinophilia and different inflammatory mediators and cytokines have already been reported in the literature. Worse CT scores and presence of systemic hyperreactive disease such as allergy and asthma are predictive of poor longterm outcome of surgical treatment as well as of previous sinus surgery. An increased number of cells expressing m-RNA for IL-5 in sinus mucosa correlated with poor outcomes. Interestingly, although surgical management of CRS has been reported to improve subjective scores better than conservative treatment, patients with poor outcomes after surgery have been demonstrated to show at least 50% of the improvement rate achieved by perioperative or postoperative topical, systemic steroid or longterm macrolide treatment.

Table 2. Spearman rank correlations between baseline concentration of interleukin-5 and improvement rate (IR) of sinusitis symptom scores

Correlation	Interleukin-5
IR - obstruction	0.58
IR - discharge	0.73*
IR - postnasal drip	0.01
IR - itching	-0.53
IR - sneezing	-0.01
IR - headache	-0.77*
IR - olfaction	-0.37
IR - cough	0.17
IR - facial swelling	0.23
IR - taste	-0.15
IR - overall score	0.74**

\*p<0.05, \*\*p<0.01

The allergic and nonallergic subgroups have been reported to show distinct cytokine profiles, whereby IL-4 and IL-5 were most distinguishing cytokines in the allergic subgroup, and IFN-gamma in the nonallergic subgroup, as detected in sinus biopsy specimens<sup>12</sup>. However, our results did not show significantly higher IL-5 levels in the sinus lavage of allergic patients, which may raise the question of difference between cytokine levels in immunohistochemical analysis and in sinus secretion. As tissue eosinophilia is a prominent feature of both allergic and nonallergic CRS, local IL-5 upregulation may be a result of local allergic inflammation, which is not always confirmed by skin prick test or serum IgE. Although allergic patients demonstrate lower subjective symptom scores at inclusion, they show worse longterm outcomes after surgery<sup>2,3</sup>. Our questionnaire revealed nonsignificantly higher subjective scores in allergic patients, which may be attributed to higher scores of sneezing in the allergic subgroup. Intranasal administration of steroid has been shown to improve outcomes in allergic patients with rhinosinusitis after endoscopic sinus surgery<sup>3</sup>. Corticosteroids efficaciously inhibit the production of a number of proallergic mediators<sup>13</sup>, including leukotrienes, histamine and cytokines such as IL-4 and IL-13, that regulate IgE production, and IL-5, which modulates eosinophil differentiation and prolongs survival within the tissues. There is a significant reduction in the markers of eosinophil and mastocyte activation in sinus fluid and in subjective sinusitis symptom scores after the endosinusal treatment<sup>14</sup>.

An increased number of cells expressing IL-5 mRNA was found in the ethmoid sinus at the time of surgery in patients who did not respond to surgical intervention<sup>2</sup>. On the contrary, we found a positive correlation between baseline IL-5 level in sinus lavage and improvement rate of sinusitis symptom score. There was a significant difference between the responders and nonresponders according to baseline IL-5 level in sinus lavage, so the results indicated a lower baseline IL-5 level in sinus lavage to be associated with lower individual improvement rate of symptom scores. This effect might be attributed to the beneficial impact of topical steroid treatment on cellular and humoral factors of the sinus mucosa in CRS patients, presumably IL-5, usually considered as a poor prognostic factor<sup>2,15</sup>.

## Conclusion

Steroid-antibiotic endosinusal treatment in patients with CRS proved efficient in reducing subjective sinusitis symptoms. The rate of improvement on endosinusal

steroid treatment is expected be higher in patients with increased levels of IL-5 in maxillary sinus lavage. Increased IL-5 levels in sinus fluid might be used as a predictor of good response to endosinusal treatment according to the Croatian guidelines for the treatment of CRS.

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### Sažetak

## PROGNOSTIČKA VRIJEDNOST IL-5 U SINUSNOM ISPIRKU KOD BOLESNIKA S KRONIČNIM MAKSILARNIM SINUSITISOM

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Cilj studije bio je procijeniti subjektivne ishode u bolesnika s kroničnim rinosinusitisom nakon endosinusne steroidne/antibiotske terapije, te ispitati pretpostavku prema kojoj bi se iz prijeterapijske razine citokina interleukina-5 u sinusnoj tekućini mogao predvidjeti odgovor na ovu vrst liječenja. U studiju je bilo uključeno 24 bolesnika sa simptomima kroničnog rinosinusitisa. Kriteriji za uključivanje u studiju bili su trajanje simptoma sinusitisa duže od tri mjeseca i zadebljanje sluznice maksilarnih sinusa za više od 6 mm, tj. maksilarni sinusitis. Bolesnici s astmom, polipozom, nedavnom infekcijom, sistemskom uporabom steroida ili prethodnom operacijom sinusa bili su isključeni. Bolesnici su endosinusno primali 2 mg deksametazona i 40 mg gentamicina po maksilarnom sinusu kroz 5 dana. Bolesnici su ocjenjivali nosne simptome i simptome specifične za kronični rinosinusitis, i sami ispunili anketni obrazac o simptomima sinusitisa na početku i 30 dana nakon ispitivanja. Koncentracija interleukina-5 analizirana je u sinusnom ispirku uzetom na početku studije. U desetoro (52,6%) bolesnika je nakon endonazalne terapije nastupilo poboljšanje s ublaženjem simptoma (bolesnici s terapijskim odgovorom), dok je u devetoro (47,4%) bolesnika stanje ostalo nepromijenjeno ili se je pogoršalo (bolesnici bez terapijskog odgovora). Značajno je poboljšanje zabilježeno za ukupni zbroj simptoma sinusitisa ( $p=0,02$ ), te za opstrukciju, postnazalni drip, glavobolju, kihanje i kašalj ( $p<0,05$ ) u cijeloj skupini. Nađena je pozitivna korelacija između bazalne razine interleukina-5 u sinusnom ispirku i stope poboljšanja sveukupnog zbroja simptoma sinusitisa ( $p<0,01$ ), kao i stope poboljšanja zbroja za nazalnu sekreciju ( $p<0,01$ ). Rezultati su pokazali kako povišene razine interleukina-5 u sinusnoj tekućini predskazuju dobar odgovor na endosinusnu steroidnu/antibiotsku terapiju.

**Ključne riječi:** *Maksilarni sinusitis – medikamentno liječenje; Kronična bolest; Sinusitis – komplikacije; Citokini – metabolizam*