Atopy as a specific predictor of response to systemic and local steroid therapy in patients with chronic rhinosinusitis without nasal polyps

ABSTRACT:

Introduction: Studies on the pathophysiology of chronic rhinosinusitis have shown an effect of IgE antibodies on the course of the disease, as well as the effectiveness of treatment. Steroid therapy remains the most prevailing method of CRS treatment.

Aim: The aim of our study was to determine the clinical response to systemic and local steroid therapy in patients with CRSsNP depending on the total IgE antibody serum concentration.

Material and methods: A total of 92 patients with CRSsNP took part in the study, where they were divided randomly into 2 groups. In group I, the patients received fluticasone propionate 800 mcg/day intranasally for 12 weeks. Patients in group II were treated with prednisone at a dose of 0.5 mg/kg/day, given orally, for 7 consecutive days and continued by another week with decreasing dosage. Both groups were evaluated prior to and following treatment using the TSS score of CRS clinical symptoms, the endoscopic Lund-Kennedy scale and the Lund-Mackay CT staging of chronic rhinosinusitis. Statistical analysis of the effectiveness of treatment was carried out in subgroups according to the total IgE serum concentrations obtained before treatment.

Results: Both groups of patients achieved statistically significant improvement in the TSS evaluation, as well as in endoscopic and CT imaging findings. In patients with a total IgE serum concentration over 100 IU/ml systemic steroid therapy showed significantly greater effect on the relief of CRS symptoms in the TSS score than intranasal steroid therapy. Analogous differences in the effectiveness of both methods were not found in patients with a normal total IgE serum concentration (<100 IU/ml).

Conclusions: A short course of systemic steroid therapy is more effective than local treatment in relieving of CRS symptoms in patients with CRSsNP with elevated serum concentration of IgE antibodies. Atopy may be considered a specific predictor of response to steroid therapy in the treatment of chronic rhinosinusitis.

KEYWORDS: atopy, chronic rhinosinusitis, IgE, steroid therapy

ABBREVIATIONS

CRS – chronic rhinosinusitis
CRSsNP – Chronic Rhinosinusitis Without Nasal Polyps
CRSwNP – Chronic Rhinosinusitis with Nasal Polyps
CT – computed tomography
EPOS – European Position Paper on Rhinosinusitis and Nasal Polyps
IgE – immunoglobulin E
MMPs – matrix metalloproteinases
TGF – transforming growth factor
TIMPs – tissue inhibitors of metalloproteinases
TSS – total symptom score

INTRODUCTION

Chronic rhinosinusitis (CRS) is defined as the presence of two or more symptoms, one of which must include nasal obstruction or rhinorrhea (anterior or posterior), with or without facial pain/pressure and/or smell disturbance for a period exceeding 12 weeks. The condition affects about 12% of the overall population [1] and is a serious health problem.

Depending on the absence or presence of polyps within the middle nasal meatus, the disorder had been, until recently, categorized as CRS with nasal polyps (CRSwNP), or CRS with no nasal polyps (CRSsNP), respectively [2, 3]. A new classification of CRS has been introduced in the European Position Paper on Rhinosinusitis and Nasal Polyps 2020 (EPOS 2020), with the disease being classified according to anatomic distribution of inflammatory lesions (localized vs. diffuse) and inflammation phenotype (primary vs. secondary) [1]. The role of pathophysiology of the inflammatory process has also been taken into account in CRS classification by identification of inflammation endotypes. From the clinical standpoint, the classification into type 2 endotype and non-type 2 endotype is of greatest significance. Simplistically, type 2 endotype is associated with eosinophilic inflammation and...
AIM

The aim of our study was to determine the clinical response to systemic and local steroid therapy in patients with CRSsNP depending on the total IgE antibody serum concentration.

MATERIAL AND METHODS

A randomized, prospective pilot study was conducted in a study group of 92 patients with CRSsNP. Inclusion criteria included the age of 18–65, diagnosis of CRS based on EPOS 2012/2020 definition, and absence of polyps in endoscopic examination of nasal cavities. Exclusion criteria consisted in confirmed immunodeficiency, mucociliary transport abnormalities, chronic fungal sinusitis, significant deformations of nasal septum, and contraindications to oral steroid therapy. Patients with a history of CRS treatment, i.e., patients receiving oral or nasal steroid therapy and antibiotic therapy within the previous 3 months and patients with a history of sinus surgeries were also excluded from the study.

The study group was randomized into two groups. Group I (n = 46) consisted of CRSsNP patients to receive nasal fluticasone propionate at a dose of 800 μg/day for the following 12 weeks. Group II patients (n = 46) were to receive oral prednisone at a dose of 0.5 mg/kg bw for 7 consecutive days and the following week, at doses tapered by 5 mg every other day.

The two groups were evaluated both prior and immediately after the treatment by performing medical history and physical examination using the TSS system to assess the severity of rhinosinusitis symptoms as reported by the patients (using a scale of 0 to 9). Furthermore, the following imaging and laboratory studies were carried out: (a) endoscopic presentation of nasal cavities using the Lund-Kennedy scoring system, (b) sinus CT scans using the Lund-Mackay scoring system (0 to 24), as well as (c) the total serum IgE concentration.

Until recently, topical steroid therapy was recommended for the treatment of patients with either CRSsNP and CRSwNP, while EPOS 2012 guidelines suggested that systemic therapy be used only in patients with CRSwNP. Currently, due to the change in CRS classification, implementation of systemic steroid therapy requires a diagnosis of type 2 inflammation, and therefore it may cover both CRSsNP and CRSwNP patients. Given the effect of steroid therapy on tissue remodeling in CRS, the purpose of our study was to determine the clinical response to nasal and oral steroid therapy CRSsNP patient groups as depending on the total blood IgE levels. Until recently, this group of patients had been excluded from systemic steroid therapy regimens.

Th2-dependent inflammatory reaction mediated by IL-4, IL-5, and IL-13 and manifested by increased IgE levels. Non-type 2 endotype corresponds to neutrophilic inflammation [2]. The main criteria taken into account in the clinical diagnostics of inflammatory endotype include tissue eosinophilia of ≥ 10 eos/HPF, blood eosinophilia of ≥ 250, or total IgE serum concentration of ≥ 100 [1]. As shown by the studies, patients with type 2 endotype are much more likely to be resistant to current treatments and more prone to disease recurrence as compared to non-type 2 patients [1, 4, 5].

IgE is one of the key mediators of type 2 inflammation. It is responsible for the transmission of the inflammatory signal and for the severity of local Th2-dependent inflammatory reaction. Once induced in the aforementioned mechanism, the process leads to tissue remodeling responsible for the severity of clinical signs, the efficacy of treatment, and disease recurrence [2]. Thus, total IgE levels are associated with the severity of the natural history of CRS [6, 7].

Being the most common anti-inflammatory regimen, steroid therapy regulates the levels of extracellular matrix metalloproteinases (MMPs) and their tissue inhibitors (TIMPs), induces epithelial regeneration and reduces the level of tissue eosinophilia [8] while also reducing the number of TGF-β1-positive cells, resulting in the nasal membrane being significantly thinner in patients on steroid therapy than in the control group.

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In order to determine the relationship between the efficacy of topical and systemic steroid therapy and serum IgE levels in patients, the study group was divided into two sub-groups according to either normal (IgE < 100 IU/mL) or increased (IgE ≥ 100 IU/mL) IgE levels. The results of the TSS, endoscopic and sinus CT examinations following topical (group I) or oral (group II) therapy were evaluated in accordance with the baseline serum IgE concentration.

Statistical analysis was performed using the Statistica software package, with continuous data being analyzed using (a) the Student’s t-test for independent samples, (b) the Student’s t-test for dependent samples, (c) the Mann Whitney’s U-test, and (d) the Wilcoxon signed-rank test.

The study was approved by the Bioethics Committee, decision no. 80/PB/2016.

RESULTS

Elevated serum IgE level subgroup (IgE ≥ 100 IU/mL)

TSS system

Following the analysis of changes in the severity of symptoms as assessed using the TSS system (nasal obstruction, anterior or posterior rhinorrhea, facial pain/pressure, smell disturbance/loss), statistically significant reductions in the total symptoms’ scores were obtained following the treatment in both groups (skewed distributions, group I: P = 0.002; group II: P = 0.04). In the group receiving nasal steroid treatment (group I), the score was reduced by 2 points as compared to 4.25 points in the oral steroid group. The difference in the improvement of symptoms between groups I and II was statistically significant (95% CI −4.01 to −0.49; P = 0.016) (Fig. 1A.).

Lund-Kennedy endoscopy scoring system

Following the analysis of changes in the severity of endoscopic symptoms (mucosal swelling and redness, nasal and sinus discharge), both groups were found to present with statistically significant reduction in symptoms following the treatment (skewed distributions, group I: P = 0.005; group II: P = 0.002). No significant difference was observed with regard to the efficacy of treatment as assessed using the Lund-Kennedy endoscopy scores between the nasal steroid treatment group and the oral steroid treatment group. The mean difference between the post- and pre-treatment values was 2.71 in the nasal steroid group vs. 3.2 in the oral steroid group (95% CI −0.92 to 2.03; P = 0.44) (Fig. 2B.).

Lund-Mackay CT scoring system

Following the analysis of changes in the severity of inflammatory symptoms in sinus CT scans, a statistically significant reduction of symptoms following the treatment was observed in both groups (group I: 95% CI 0.52 to 3.67, P = 0.01; group II: 95% CI −0.07 to 1.73, P = 0.04). No significant difference was observed with regard to the efficacy of treatment as assessed using the Lund-Mackay score between the nasal steroid treatment and the oral steroid treatment groups. The mean difference between the post- and pre-treatment values was 0.57 in the nasal steroid group vs. 2.09 in the oral steroid group (skewed distribution; P = 0.11) (Fig. 3B.).

DISCUSSION

It is increasingly recognized that CRS covers a wide range of disorders with varied clinical presentations and pathogenic mechanisms. Identification of separate CRS phenotypes and endotypes affects prognosis and facilitates therapeutic decision-making.

Until recently, systemic steroid therapy was limited to patients in whom severe polyp lesions resistant to topical steroids had been found within the nasal cavities. No indications for systemic steroid treatment in CRSsNP patients had been listed in the EPOS 2012 guidelines. This approach has changed since 2020, when new
Most reports available in literature describing endoscopic examination of nasal cavities, both before and after steroid therapy in patients with CRS, also suggest very high efficacy of both treatments in reducing inflammation [11–13]. A statistically significant improvement was observed in the results of nasal endoscopy examinations performed 2–3 weeks following oral steroid treatment compared to the results obtained in the placebo group as carried out by Alobid [14] and Vaidyanathan [15] (P < 0.0001); in the latter study, the effect was maintained for 3–6 months after treatment completion. In our endoscopic examination of nasal cavities, both therapeutic modalities significantly improved patient outcomes by approximately 3 points in the Lund-Kennedy score. At the same time, no statistically significant advantage was observed in the efficacy of any of the modalities irrespective of the IgE level observed in the patient.

An analysis of the studies assessing the outcomes of steroid therapy, using the Lund-Mackay CT scoring system, revealed that the treatment significantly reduced the severity of inflammatory changes in sinus CT scans. This effect was observed after both oral and nasal steroid therapy [15]. In our study, both treatments led to a significant reduction in the inflammatory lesions as assessed using the Lund-Mackay CT scoring system in both the increased IgE level and the normal IgE level groups.

Both topical and systemic steroid therapy brought about better mean improvement in the atopic subgroup (3.2- and 3.25-point reduction respectively) as compared to the subgroup of patients with normal IgE levels (0.57- and 2.09-point reduction respectively); however, the differences were not statistically significant.

Nonetheless, literature contains isolated reports on the efficacy of nasal steroids in patients with CRSsNP in reducing subjective symptoms alone, without any improvement being observed in nasal endoscopy or sinus CT scans [16]. These observations differ from those made in our study.

European guidelines for the treatment of CRS, highlighting the role of disease pathogenesis, were published. According to the guidelines, one of the prognostic factors for treatment response consisted of patient’s serum IgE levels. Therefore, in this study, we attempted to evaluate the efficacy of topical and systemic steroids in CRS patients depending on their serum IgE levels.

As part of the randomized trial, the efficacy of nasal fluticasone propionate treatment and oral prednisone treatment were assessed in CRS patients randomly allocated to treatment groups. Statistically significant subjective improvement of post-treatment TSS scores, as compared to pre-treatment scores, was observed in both treatment groups. Moreover, reduction in Lund-Kennedy endoscopy scores of CRS symptoms and Lund-Mackay CT scores of inflammatory lesions were observed in both groups.

Most studies focusing on nasal and oral steroidotherapy shows positive effects of both modalities with regard to subjective nasal symptoms, improved nasal patency, smell, and taste, albeit mainly in CRSwNP patients [10]. Kirtsreeakul [11] demonstrated a statistically significant difference (P < 0.0001) in TSS outcomes following the administration of oral steroid, i.e. prednisolone, compared to the placebo group. Similar result was observed in our study with statistically significant improvement in the TSS occurring after both nasal and oral steroid therapy.

The next step consisted in an attempt at determining whether the initial pre-treatment serum IgE levels had any effect on treatment efficacy. The study revealed a statistically significant advantage of general steroid therapy over topical treatment in reducing the subjective symptoms of CRS, as assessed using the TSS system in patients with baseline serum IgE levels of above 100 IU/mL. The mean TSS reduction following prednisone treatment was 4.25 points as compared to 2 points after nasal steroid. Whereas, no significant differences in the efficacy of both modalities, as measured using the TSS system, were observed in patients with normal baseline serum IgE levels.

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![Fig. 2. Changes in the severity of symptoms as assessed using the Lund-Kennedy endoscopy scoring system following topical (group I) and oral (group II) steroid therapy in patients with IgE ≥ 100 IU/ml (A) and patients with IgE < 100 IU/ml (B).](Image)
In conclusion, our analysis appears to suggest that the IgE level in patients is important in predicting the response to treatment in the CRS group. In subjects with serum IgE levels of above 100 IU/mL, one may expect better improvement in the subjective rhinosinusitis symptoms following systemic steroid therapy as compared to topical steroid therapy.

Since there are significant differences between chronic rhinosinusitis with and without nasal polyps regarding the specific cellular infiltrate, cytokine and mediator profiles, immune responses and bone remodeling, no systemic steroid therapy had been recommended until the latest version of the EPOS consensus as published in 2020. Short courses of systemic steroids, previously reserved mainly for patients with CRSwNP, have earned their place in the treatment of CRSsNP patients with elevated serum IgE levels. Moreover, they are more effective in reducing the troublesome symptoms (i.e., nasal obstruction, rhinorrhea, headache, smell disorders) than local steroid therapy, as indicated by our research and recent studies on the topic [17, 18]. In the context of CRS, atopy appears to be a specific predictor of CRS severity, linked to specific histopathological variables including increased eosinophilic aggregates [19]. In the future, allergic conditions may become useful means for identifying atopic endotype in CRS patients.

Identification of CRS endotypes changes our outlook on CRS treatment; it plays an increasingly important role in providing the most appropriate treatments for individual patients, including the possibility of biological treatment using anti-IgE and anticytokine antibodies which are becoming increasingly available worldwide [20–22].

**REFERENCES**


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