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Original Article

Two-Track Medical Treatment Strategy According to the Clinical Scoring System for Chronic Rhinosinusitis

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ABSTRACT

Purpose: The previously reported Japanese clinical scoring study (JESREC) suggests that chronic rhinosinusitis (CRS) can be divided into 4 subtypes according to the degree of eosinophilic CRS (ECRS) and offers the information regarding the prognosis of CRS to clinicians. However, this scoring system has not yet been validated by an immunological study and needs to provide treatment guidelines based on underlying immunologic profiles. We investigated the immunologic profile of each CRS subgroup according to the JESREC classification and suggest its clinical application.
Methods: A total of 140 CRS patients and 20 control subjects were enrolled. All patients were classified into 4 groups according to the JESREC (non-, mild, moderate and severe ECRS). Nasal tissues were analyzed for mRNA expression of major cytokines (IL-5, IL-10, IL-13, IL-17A, IL-22, IL-23p19, IFN-γ, periostin, thymic stromal lymphopoietin [TSLP] and ST2), major chemokines (CCL11, CCL24, CXCL1 and CXCL2), transcription factors (T-bet, GATA3, RORC and FOXP3) and COL1A1 for type I collagen. Protein levels of 3 major cytokines (IL-5, IL-17A and IFN-γ) were also measured by multiplex immunoassay. Principal component analysis (PCA) was conducted to investigate the overall profile of multiple mediators.
Results: The moderate/severe ECRS showed up-regulation of type 2-related mediators (IL-5, IL-13, periostin, TSLP and ST-2), whereas INF-γ (type 1 cytokine) and CXCL1 (neutrophil chemokine) expressions were increased in non-/mild ECRS compared with moderate/severe ECRS. The JESREC classification reflected an immunological endotype. In PCA data, PCA1 indicates a relative type 2 profile, whereas PCA2 represents a type 1/type 17-related profile. In this analysis, mild ECRS was indistinguishable from non-ECRS, whereas moderate to severe ECRS showed a distinct distribution compared with non-ECRS. The JESREC classification could be divided into 2 categories, non-/mild vs. moderate/severe ECRS based on underlying immunological analyses.
Conclusions: The CRS clinical scoring system from the JESREC study reflects an inflammatory endotype. However, the immunologic profile of mild ECRS was similar to that of non-ECRS. Therefore, we propose type 2-targeted medical treatment for moderate to severe ECRS and type 1/type 17-targeted for non-ECRS and mild ECRS as the first treatment option.

Keywords: Nasal polyps; rhinitis; sinusitis; validation studies; therapeutics; physicians

INTRODUCTION

Chronic rhinosinusitis (CRS) is a common chronic inflammatory disease of the nasal and paranasal mucosa.[1] It usually causes substantially impaired quality of life, reduces workplace productivity and is related to substantial direct and indirect economic cost.[2] CRS is currently defined as subgroups of patients based on nasal endoscopic findings, either with nasal polyps (CRSwNP) or without nasal polyps (CRSsNP).[1] Endoscopic sinus surgery (ESS) is an effective intervention for patients with medically recalcitrant CRS. However, although ESS has been performed appropriately, some patients show symptom persistence and disease recurrence, or often need revision surgeries.[3-5] Therefore, clinicians have been interested in the development of biomarkers to determine which CRS patients would recur after ESS.

In the past, CRS was thought to be a dichotomous disease according to the clinical phenotype (CRSsNP and CRSwNP),[6-8] but the concept has recently changed to the disease continuum that has a broad inflammatory spectrum.[9-12] Thus, to date, the inflammatory endotype is more useful to determine the clinical course and therapeutic decision on CRS patients. However, only a few endotyping systems that clinicians can use in their clinics have been suggested, because most of the endotyping systems require an invasive procedure to harvest nasal tissues and complicated bench works.

Recently, a Japanese group developed a novel clinical scoring system for CRS, called the JESREC scoring system, based on a large number of CRS patients (1,716).[5] According to this system, clinicians can classify CRS patients into non-ECRS (eosinophilic CRS), mild ECRS, moderate ECRS and severe ECRS based on clinical parameters including CT findings and blood eosinophilia. These subgroups showed a significant correlation with both the recurrence and refractoriness. Moreover, clinicians can easily use this scoring system using nasal endoscopic exam, peripheral blood sampling, sinus CT findings, and history of bronchial asthma and aspirin/nonsteroidal anti-inflammatory drug (NSAID) intolerance. It is notable that this algorithm could give useful information to clinicians for predicting the refractoriness of CRS without a complicated endotyping process. However, the molecular inflammatory profile of the JESREC scoring system has not yet been established. Given that two-track treatment strategy (type 2 vs. type 1/type 17) has been suggested in CRS, 4 subtypes of CRS from JESREC study need to be simplified into 2 subtypes. Therefore, in the present study, we investigated whether the JESREC scoring system is relevant to the molecular inflammatory profiles and suggested a new medical treatment strategy for CRS including emerging biologic agents.

MATERIALS AND METHODS

Subjects

Sinonasal tissues were obtained from patients with CRS during routine ESS. The diagnosis of CRS was based on personal medical history, physical examination, nasal endoscopy and CT findings of the nasal cavity with sinuses according to the 2012 European position paper on rhinosinusitis and nasal polyps (EPOS) guidelines.[1] Patient exclusion criteria were as follows: 1) younger than 18 years old; 2) previous treatment with antibiotics, systemic or topical corticosteroids, or other immune-modulating drugs up to 4 weeks before surgery; and 3) conditions such as unilateral rhinosinusitis, antrochoanal polyps, allergic fungal sinusitis, cystic fibrosis or immotile ciliary disease. Control tissues were obtained during

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other rhinologic surgeries such as skull base, lacrimal duct or orbital decompression surgery and from patients without any sinonasal diseases. We obtained uncinate tissue from control and CRS patients. We also took NP tissues in CRSwNP patients. All enrolled patients were classified into subgroups according to the algorithm of JESREC study[5]: control, non-eosinophilic CRS (non-ECRS), mild eosinophilic chronic rhinosinusitis (ECRS), moderate ECRS and severe ECRS. Subgrouping is conducted by several clinical factors including bilateral disease sites, NP, sinus CT findings, eosinophilia in peripheral blood and comorbidity (bronchial asthma and aspirin-exacerbated respiratory disease/NSAID-exacerbated respiratory disease). Meanwhile, histological eosinophilic CRS was defined as > 10% eosinophils per high-power field (HPF).[13] All patients provided a written form of informed consent for study participation, and this study was approved by the Institutional Review Board of Seoul Metropolitan Government-Seoul National University Boramae Medical Center.

Quantitative real-time RT-PCR

We analyzed the mRNA expression levels of cytokines (IL-5, IL-10, IL-13, IL-17A, IL-22, IL-23p19, IFN-γ, periostin, thymic stromal lymphopoietin [TSLP], ST2 and TGF β2), inflammatory markers (CCL11, CCL24, CXCL1, CXCL2 and COL1A1) and major transcription factors (GATA-3, RORC, T-bet and FOXP-3) by quantitative real-time PCR (qRT-PCR). Total RNA was extracted from tissue samples with TRI reagent (Invitrogen, Carlsbad, CA, USA). One microgram of total RNA was reverse-transcribed to cDNA with a cDNA Synthesis Kit (amfiRivert Platinum cDNA Synthesis Master Mix, GenDEPOT, Barker, TX, USA). The qRT-PCR was performed with a LightCycler 480 SYBR Green I Master (Roche, Mannheim, Germany). For analysis of IL-5 (Hs01548712_g1), IL-10 (Hs00961622_m1), IL-13 (Hs00174379_m1), IL-17A (Hs00174383_m1), IL-22 (Hs01574154_m1), IL-23p19 (Hs00900828_g1), IFN-γ (Hs00989291_m1), periostin (Hs01566734_m1), TSLP (Hs00263639_m1), ST2 (Hs00545033_M1), CCL11 (Hs00237013_m1), CCL24 (Hs00171082_m1), CXCL1 (Hs00236937_m1), CXCL2 (Hs00601975_m1), and GAPDH (Hs02758991_g1), pre-developed assay reagent (PDAR) kits of primers and probes were purchased from TaqMan assays (Life Technologies Korea, Seoul, Korea). COL1A1 (QT00037793) was also purchased from QIAGEN Korea Ltd. (Seoul, Korea). Also, the quantitative real-time PCR assay was performed with appropriate primers that specifically amplified T-bet, GATA-3, RORC, FOXP3and TGF β2. Primers were as follows: T-bet, 5′-GTCAATTCCTTGGGGGAGAT-3′ for the forward primer and 5′-TCATGCTGACTGCTCGAAAC-3′ for the reverse primer; GATA-3, 5′-ACCACAACCACACTCTGGAGGA-3′ for the forward primer and 5′-TCGGTTTCTGGTCTGGATGCCT-3′ for the reverse primer; RORC, 5′-GCTGTGATCTTGCCCAGAACC-3′ for the forward primer and 5′-CTGCCCATCATTGCTGTTAATCC-3′ for the reverse primer; FOXP3, 5′-ACAGTCTCTGGAGCAGCAGC-3′ for the forward primer and 5′-CCACAGATGAAGCCTTGGTC-3′ for the reverse primer; and TGF β2, 5′-TGGATGCGGCCTATTGCTTTA-3′ for the forward primer and 5′-GCGGAAGTCAATGTACAGCTGCCGC-3′ for the reverse primer, and GAPDH, 5′-CATGGGTGTGAACCATGAGAA-3′ for the forward primer, 5′-GGTCATGAGTCCTTCCACGAT-3′ for the reverse primer. GAPDH was measured as a housekeeping gene for normalization. Cycling conditions were 95°C for 5 minutes, followed by 60 cycles at 95°C for 15 seconds, 55°C for 20 seconds, and 72°C for 20 seconds. Data were analyzed with Sequence Detection Software version 1.9.1 (Applied Biosystems, Foster City, CA, USA). Relative gene expression was calculated by the comparative $2^{-\Delta\Delta CT}$ method.

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Measurement of major cytokines

The protein concentrations for tissue extracts were determined using the Pierce 660 nm Protein Assay Kit (ThermoScientific Inc., NY, USA). All the protein levels in tissue homogenate were normalized to the concentration of total protein (mg/mL). Samples were thawed at room temperature and vortexed to ensure well-mixed sample. Cytokine analysis kits (IL-5, IL-17A and IFN-γ) were obtained from R&D systems (Cat. No. LMSAHM) and data were collected using Luminex 100 (Luminex, Austin, TX, USA). Data analysis was performed using the MasterPlex QT version 2.0 (MiraiBio, Alameda, CA, USA). Sensitivity of each cytokine is as follows: IL-5 (0.5 pg/mL), IL-17A (1.8 pg/mL) and IFN-γ (0.4 pg/mL). All assays were run in duplicate according to the manufacturers' protocol.

Statistical analysis

Statistical analyses were performed using IBM SPSS 20 (SPSS, Inc., Chicago, IL, USA) and GraphPad Prism software 6.0 (GraphPad Software Inc., La Jolla, CA, USA). For comparisons among more than 2 groups, the Kruskal-Wallis test was initially used to identify the significant difference, and then, the Mann-Whitney U test was also executed to confirm significance between 2 groups. For adjustment the significance level for each comparison, Bonferroni adjustment was used. A multivariate analysis of data for mRNA expression levels was conducted using principal component analysis (PCA). The significance level was set at $\alpha = 0.05$ ($^{*}P < 0.05$, $^{\dagger}P < 0.01$, and $^{\ddagger}P < 0.001$).

RESULTS

Characteristics of the study population

We enrolled total 140 CRS patients and 20 control subjects. Demographic and clinical characteristics of the enrolled subjects in this study are presented in **Table**. According to the JESREC scoring system, the proportion of each subgroup was as follows: non-ECRS, 50.7% (n = 71); mild ECRS, 17.1% (n = 24); moderate ECRS, 23.6% (n = 33); and severe ECRS, 8.6% (n = 12). There was no significant difference in Lund-Mackay CT score or the presence of atopy/nasal polyp among 4 groups. The ratio of histological eosinophilic CRS increased consistently with the progression from clinical non-ECRS to severe ECRS based on the JESREC system. In non-ECRS, 23.9% patients were confirmed with histologic eosinophilic CRS. Mild, moderate and severe ECRS groups had 45.8%, 61.3% and 71.4% of histologic eosinophilic CRS, respectively.

Table. Patient characteristics and type of method

Total No. of subjects	Control (n = 20)	Non-ECRS (n = 71)	Mild ECRS (n = 24)	Moderate ECRS (n = 33)	Severe ECRS (n = 12)
Age (yr), mean (SD)	45 (19)	49 (15)	47 (14)	46 (14)	52 (13)
Sex (male), No. (%)	14 (70)	46 (64.8)	22 (91.7)	24 (72.7)	5 (41.7)
Asthma, No. (%)	0 (0)	2 (2.8)	0 (0)	3 (9.1)	12 (100)
Atopy, No. (%)	5 (25)	21 (29.6)	10 (41.7)	16 (48.5)	5 (41.7)
Aspirin sensitivity, No.	0	0	0	0	2
Lund-Mackay CT score	0 (0)	12.7 (6.1)	14.5 (4.3)	13.2 (5.2)	16.8 (6.6)
Blood eosinophil % (SD)	2.28 (1.12)	2.43 (1.72)	4.59 (2.09)	7.61 (2.75)	10.6 (4.11)
CRSsNP, No. (%)	0	37 (52.1)	5 (20.8)	16 (48.5)	4 (33.3)
CRSwNP, No. (%)	0	34 (47.9)	19 (79.2)	17 (51.5)	8 (66.7)
Histologic eosinophilic CRS, No. (%)	0	16 (23.9)	11 (45.8)	19 (61.3)	10 (83.3)

ECRS, eosinophilic chronic rhinosinusitis; SD, standard deviation; CT, computed tomography; CRSsNP, chronic rhinosinusitis without nasal polyps.

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Expression of inflammatory cytokines and chemokines according to different CRS groups

To investigate the immunological profile, we performed qRT-PCR analysis on sinonasal tissues (UP from control, CRSsNP and NP from CRSwNP). Besides, type 2-associated cytokine profiles including IL-5, IL-13, periostin, TSLP, ST-2 (receptor for IL-33) and CCL24 showed an up-regulated expression tendency from control to severe ECRS (**Fig. 1**). Meanwhile, type 17-related cytokines such as IL-17A, IL-22 and IL-23p19 mRNA expression showed a significant upregulation in non-ECRS and mild ECRS or moderate ECRS than

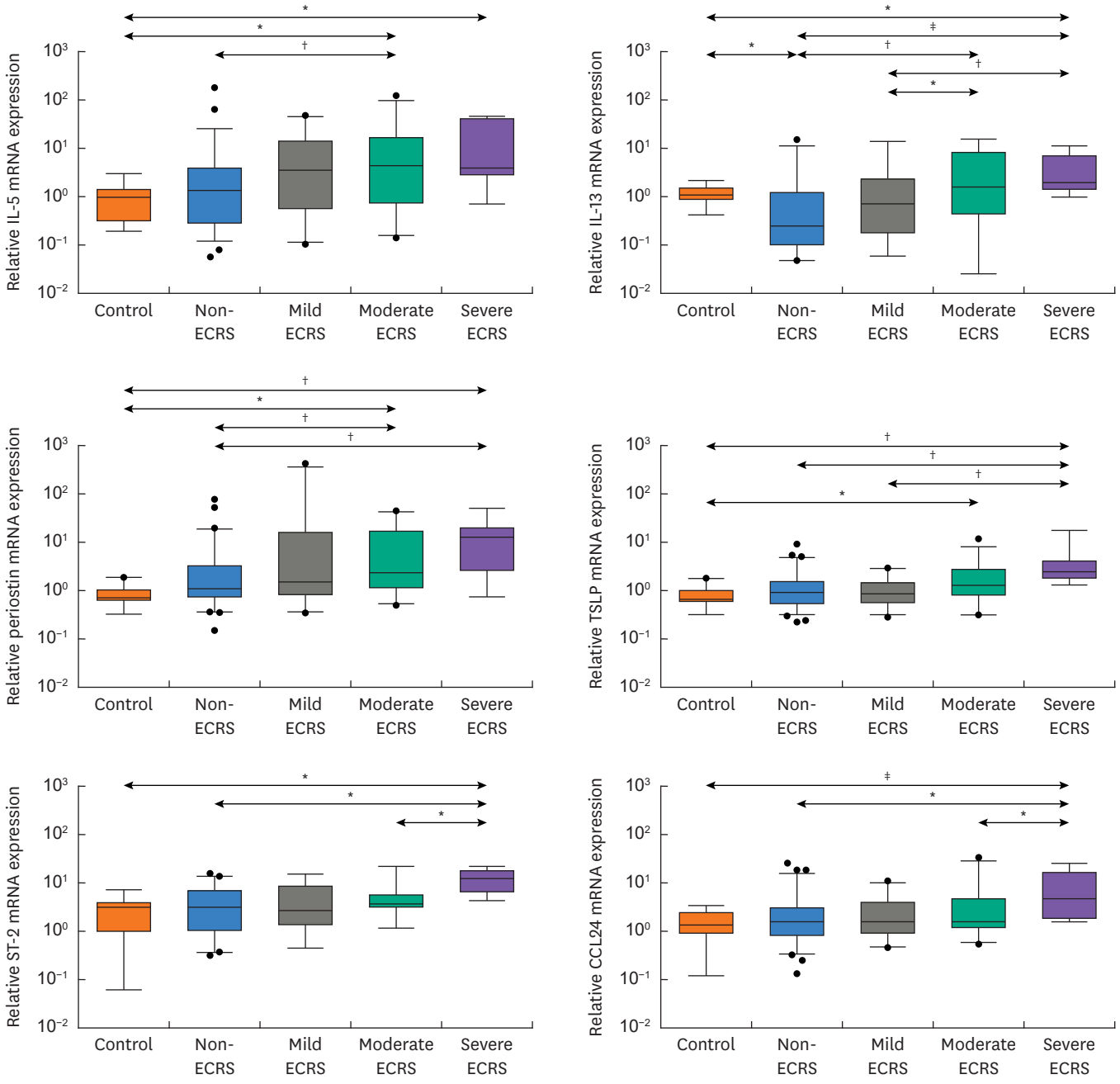

Fig. 1. Expression of type 2-related cytokines in nasal tissues according to clinical CRS classification.
CRS, chronic rhinosinusitis; ECRS, eosinophilic chronic rhinosinusitis; IL, interleukin; TSLP, thymic stromal lymphopoietin.
*P < 0.05, †P < 0.01, and ‡P < 0.001.

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controls and severe ECRS. CXCL1, a neutrophils-recruiting chemokine, was overexpressed in non-ECRS and mild ECRS compared with moderate ECRS. Additionally, type 1 cytokine, INF-γ mRNA expression was significantly more decreased in moderate and severe ECRS groups compared with control subjects and non-ECRS group (**Fig. 2**). An anti-inflammatory cytokine, IL-10, demonstrated increasing tendency towards severe ECRS. We also evaluated the protein levels of cytokine profiles (IL-5, IL-17A and IFN-γ) in different CRS groups. Expression levels of IL-5 was significantly increased from controls to severe ECRS, whereas

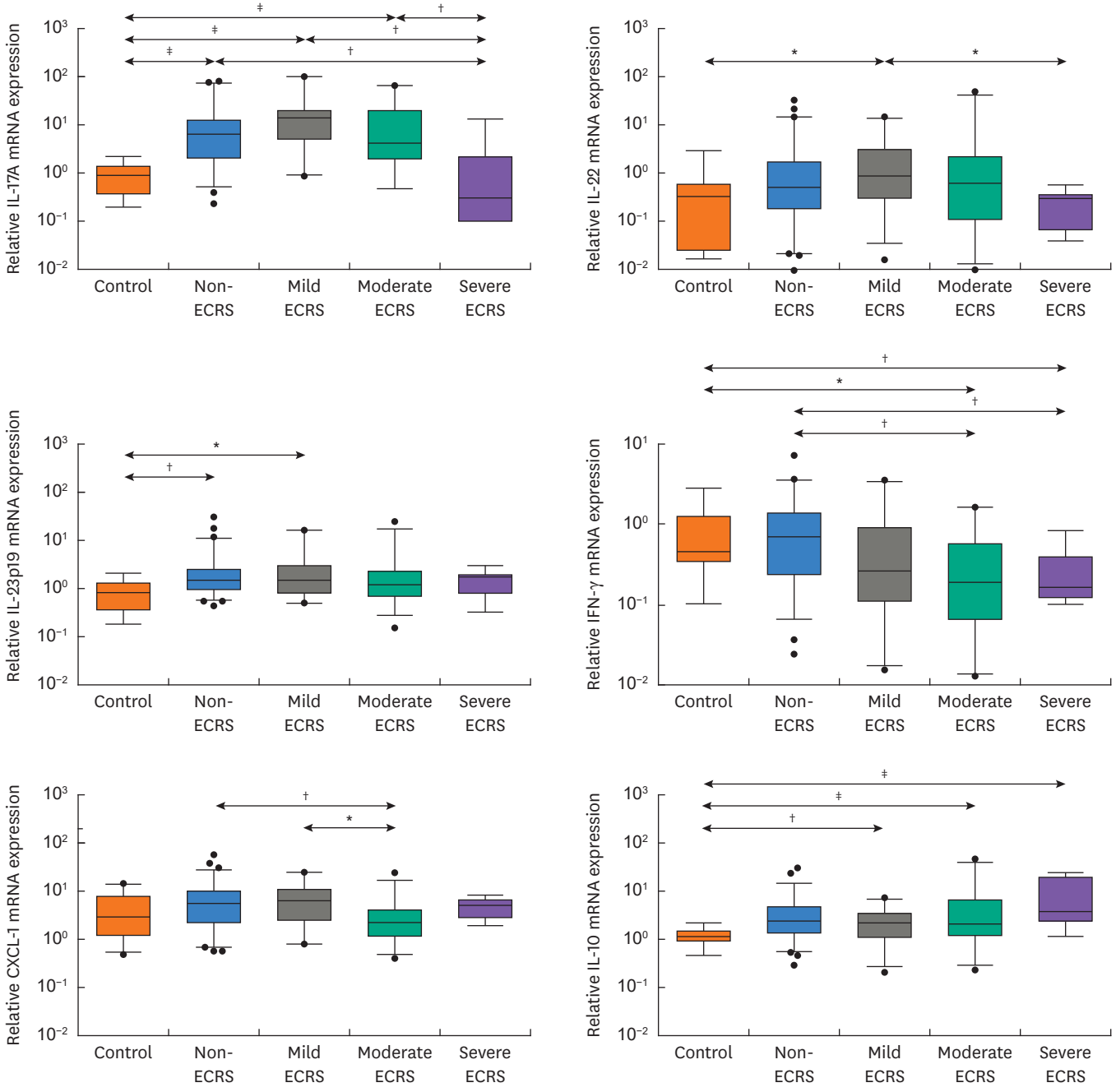

Fig. 2. Expression of type 1- or type 17-related cytokines in nasal tissues according to clinical CRS classification.
CRS, chronic rhinosinusitis; IL, interleukin; ECRS, eosinophilic chronic rhinosinusitis.
*P < 0.05, †P < 0.01, and ‡P < 0.001.

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IL-17A and IFN-γ were significantly more decreased in severe ECRS groups compared with non- and mild ECRS groups (**Fig. 3**).

Expression of tissue remodeling mediators and transcription factors according to different CRS groups

In the analysis of tissue remodeling mediators, there was no difference in the expression of COL1A1 mRNA levels among CRS groups. However, the expression of TGF-β2 mRNA levels was significantly more increased in non-ECRS and mild ECRS, compared with controls ($P = 0.0011$ and $P = 0.0108$, respectively). We also found that the GATA-3 levels were significantly less expressed in non-ECRS and mild ECRS groups than in controls, whereas these groups showed a significantly more increased expression of T-bet levels compared with controls (**Fig. 4**). However, there were no differences in the levels of RORC or FOXP3.

Principal component analysis (PCA)

To investigate the overall immunologic profile according to the different CRS groups, we performed the PCA (**Fig. 5**). The first component (PCA1) accounted for 15.9% of the variance in the dataset, and its greater discriminators were IL-10, TSLP, IL-13 and CCL24 (in order). The second component (PCA2) accounted for 14.4% of the variance in the dataset, and its greater discriminators were CXCL1, IFN-γ and IL-17A (in order). Thus, the PCA1 component represented a predominant type 2-related immunologic profile, whereas PCA2 component

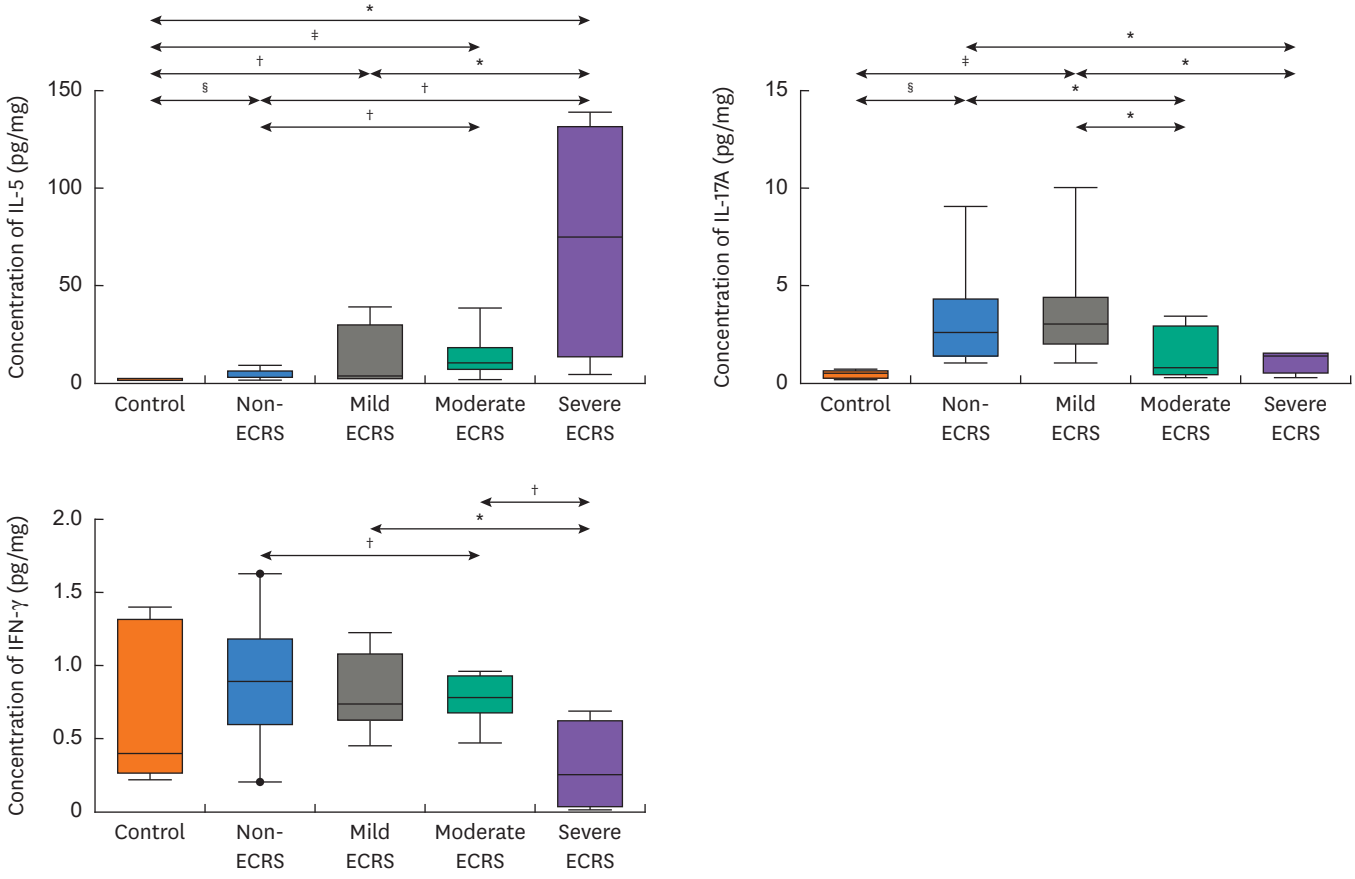

Fig. 3. Expression of IL-5, IL-17A and IFN-γ in nasal tissues according to clinical CRS classification.
IL, interleukin; CRS, chronic rhinosinusitis; ECRS, eosinophilic chronic rhinosinusitis.
*$P < 0.05$, †$P < 0.01$, and ‡$P < 0.001$.

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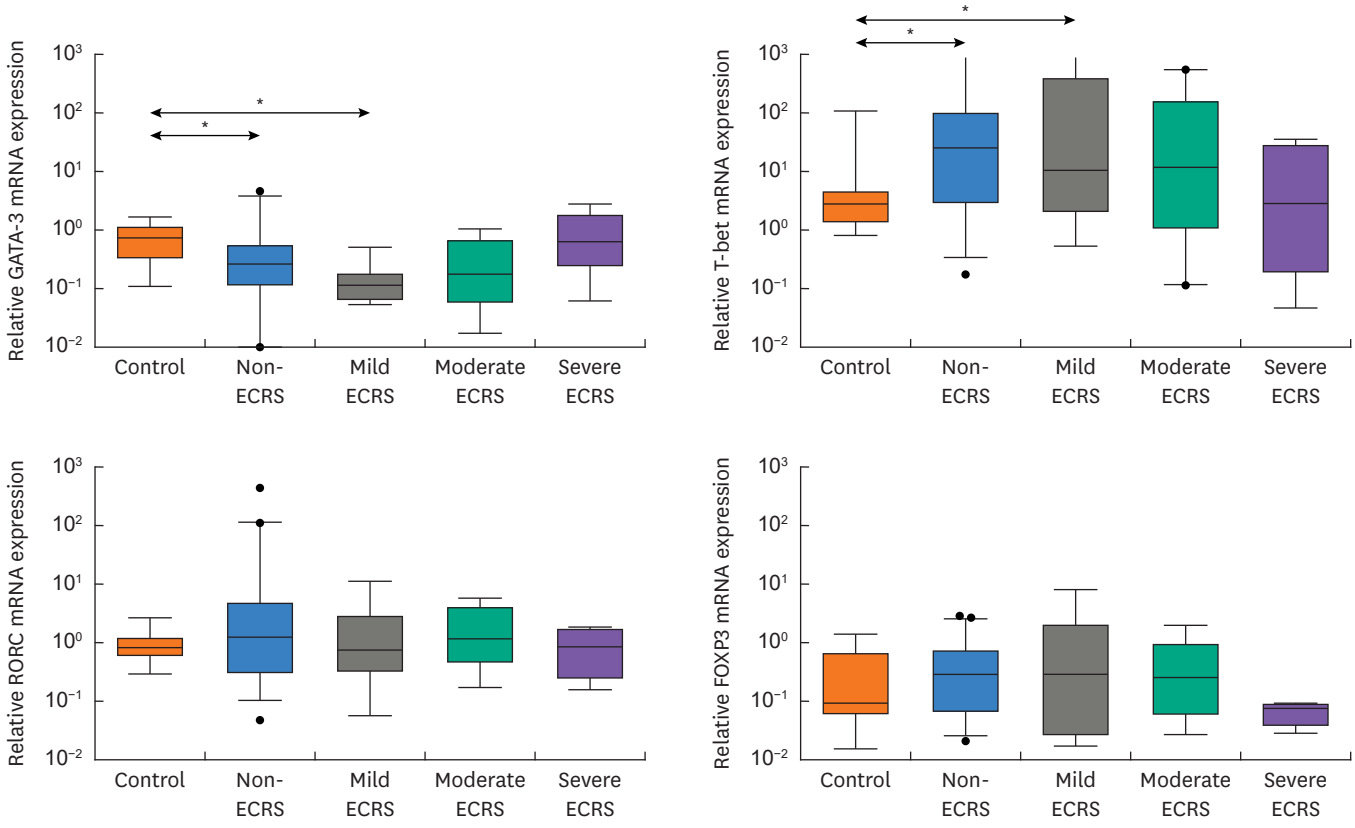

Fig. 4. Expression of transcription factors in nasal tissues according to clinical CRS classification.
CRS, chronic rhinosinusitis; ECRS, eosinophilic chronic rhinosinusitis.
*$P < 0.05$.

indicated a relative type 1/type 17-related immunologic profile. This PCA data revealed that PCA1 and PCA2 could help discriminate between non-/mild ECRS and moderate/severe ECRS. Moreover, we found that moderate and severe ECRS groups showed a high type 2 and low type 1/type 17-related expression, whereas mild and non-ECRS have a similar immunologic profile with high type 1/type 17 and low type 2-related expression.

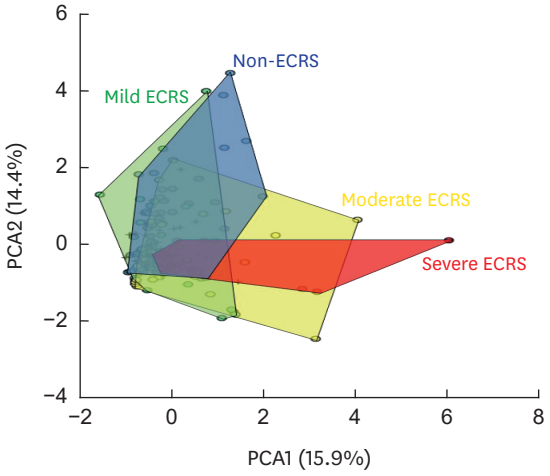

Fig. 5. PCA consisted of the first and second PCA components using multiple inflammatory mediators according to clinical CRS classification.
PCA, principal component analysis; CRS, chronic rhinosinusitis; ECRS, eosinophilic chronic rhinosinusitis.

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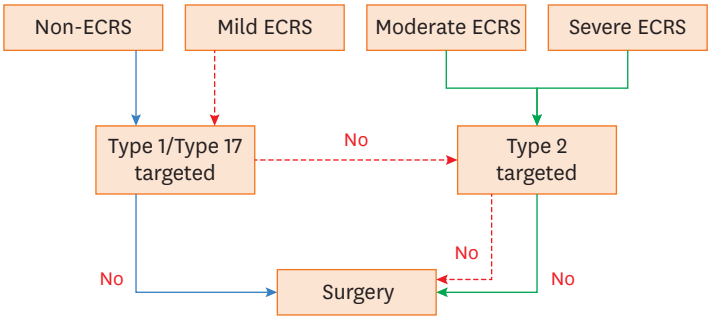

Fig. 6. Clinical therapeutic strategy for CRS according to clinical CRS classification.
CRS, chronic rhinosinusitis; ECRS, eosinophilic chronic rhinosinusitis.

DISCUSSION

To date, intranasal or systemic steroids, antibiotics and nasal irrigation are considered a main treatment for patients with CRS.[1,14] Besides these, aspirin desensitization has been used as an adjunctive treatment in patients with CRSwNP who have aspirin-exacerbated respiratory disease.[15-17] Sometimes, CRS patients who have a medically refractory condition underwent ESS to improve mucociliary clearance and restore patency of sinus drainage tracts. However, despite the advance in surgical techniques and the use of intranasal steroids after ESS, some patients suffer from recurrence of their disease. This indicates that there is an extreme diversity on CRS regarding the immunologic endotypes. Thus, novel therapeutics are needed to treat these medically and/or surgically refractory CRS patients.

Currently, several studies from Western counties have been suggested that there are distinct immunologic mechanisms in patients with CRSsNP (predominant type 1 milieu) and CRSwNP (type 2-skewed eosinophilic inflammation).[6-9] Meanwhile, the inflammatory endotype of Asian subjects is primarily dominant neutrophilic inflammation with type 1/type 17 immune response, but this endotype is minority in Western.[10-12] Moreover, a cluster analysis study with phenotype-free approach has identified that CRS patients have 10 distinct inflammatory endotypes, which are correlated with phenotype and that these endotypes comprise 4 clusters with low IL-5 and 6 clusters with moderate to high IL-5.[18] Another cluster analysis study also suggested 7 CRS clusters according to the immunologic characteristics and treatment outcomes.[19] These indicate that CRS shows remarkable heterogeneity at the molecular level and that the characteristics of each endotypes may have a serial continuum of immunologic profile.

However, NP tissues also frequently recur after surgery in Asian CRSwNP, and patients with these recurrent NP show prominent tissue eosinophilic infiltration.[20] Some studies from Japan showed that CRSwNP patients with ≥ 70 eosinophils/HPF had the highest recurrence rate compared to other groups with lower tissue eosinophilia.[21,22] Thus, consistent with Western NP, tissue eosinophilic status can provide information regarding prognosis of CRSwNP in Asian populations. However, there is still no clear consensus about the criteria of ECRS. In addition, the lab-based methods using ECP/MPO ratio or periostin, has not been validated as a single useful predictable biomarker.

Recently, the novel classification system of CRS was suggested by a Japanese group through multi-center studies.[5] This classification named the JESREC scoring system may be used as a

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tool that can easily predict clinical course. The major advantage of the JESREC scoring system is that it can be easily measured with clinically available parameters. The sinus CT scan, eosinophil count of peripheral blood and nasal endoscopy are sufficient to diagnose ECRS, and only a history of asthma or aspirin intolerance is additionally needed for 4 subgroupings of ECRS. Thus, the JESREC scoring system enables clinicians to classify ECRS without any invasive procedure such as biopsy or surgery. In addition, these 4 groups are well correlated with the rate of recurrence and refractoriness in CRS. Among those, moderate and severe ECRS groups are considered as refractory CRS.

Despite these advantages, the JESREC scoring system still need a verification to be used as a diagnostic tool of CRS, because it has relatively low specificity (sensitivity: 83%, specificity: 66%) for discrimination between non-ECRS and ECRS. It means a significant number of immunologic non-ECRS patients may be included in the ECRS group. Thus, in the present study, we investigated and compared the immunologic profile according to the JESREC classification. In accordance with the findings of previous studies,[6-12] the present study confirmed that there were significant differences in the inflammatory profile of the 4 CRS subgroups classified by the JESREC scoring system. Specifically, moderate and severe ECRS is related to IL-5, IL-13, periostin, TSLP and ST-2, representing type 2 cytokines, whereas non-ECRS relates to type 1/type 17-associated cytokines. From our analysis, mild ECRS was immunologically similar to non-ECRS, which is attributed to the relatively low specificity of the JESREC classification system. Furthermore, in contrast with previous studies,[23-25] we observed that the level of IFN-γ as a type 1 cytokine was not increased in non-ECRS and mild ECRS patients, compared with control subjects. We thought that this discrepancy may be caused by using different nasal tissues for the evaluation of IFN-γ between prior studies and our study. The prior studies have used inferior turbinate or ethmoidal mucosa as controls, whereas we used UP tissues.[26] In addition, a recent study supported our findings and it also similarly described the IFN-γ expression, which did not significantly elevate in CRSsNP.[27]

To date, the concept of personalized treatment of CRS is based on its endotypes, because CRS shows highly heterogeneity which causes different therapeutic responses.[25,28] However, the current therapeutic strategy for CRS has roughly 2 treatment approaches. One approach is the use of intranasal/systemic corticosteroids in ECRS patients treated with medical management alone or surgery plus medical management.[29-31] Several studies have revealed that CRS patients with a higher expression of type 2-cytokines (IL-5 high and IL-13 high) tend to shows a better clinical benefit from corticosteroids.[32,33] In this condition, physicians could also consider the use of biologics (type 2 targeted) for treatment of ECRS. Other approach for non-ECRS patients is intranasal corticosteroid plus antibiotic therapy followed by surgery.[34,35] As with asthma, it is recognized that non-ECRS show a steroid-resistant phenotype. Thus, type 2 biologics would be ineffective in these patients. Interestingly, our PCA findings revealed that mild ECRS patients showed more similar inflammatory patterns to non-ECRS patients rather than moderate or severe ECRS. In addition, moderate and severe ECRS patients have similar inflammatory patterns on PCA findings. Thus, we propose the 2-track treatment strategy (**Fig. 6**). Moderate and severe ECRS patients are treated by type 2-targeted medication, such as systemic corticosteroids or anti-eosinophilic or anti-type 2 biologic agents. On the other hand, non-ECRS and mild ECRS patients are managed with sufficient antibiotic therapy including a long-term macrolide, followed by surgery or newly emerging anti-type 17 biologic agents. Meanwhile, type 2-targeted therapy could also be tried in some mild ECRS patients when antibiotics were not effective, because a part of mild ECRS may belong to a type 2 inflammatory category (**Fig. 6**). However, the long-term results of the

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2-track treatment strategy have not been obtained yet. Therefore, further studies are needed to establish the consensus of the 2-track treatment strategy on CRS patients.

In conclusion, the JESREC clinical CRS classification system well reflects immunologic characteristics of CRS patients. Based on this classification, we propose a 2-track treatment strategy for CRS patients. Although our findings have no long-term prognosis after treatment according to the clinical CRS classification, this strategy might help clinicians make a better decision to treat individual CRS patients based on clinical parameters without tissue-based inflammatory endotyping.

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