The Practical Guideline for the Management of Allergic Rhinitis in Japan is the standard guideline in Japan. The first edition was published in 1993, and the 9th edition was released in 2020. In this latest edition, the figure showing the mechanism of allergic rhinitis was revised in which type 2 immune response has a crucial role. Type 2 immune response is characterized by the production of type 2 cytokines including IL-4, IL-5, IL-13 and IL-31. For example, we showed that approximately two thirds of peripheral blood mononuclear cells from patients with Japanese cedar and cypress pollinosis (JCCP) produced IL-31 in response to allergen suggesting that IL-31 is not essential for the onset of JCCP. On the other hand, patients positive for IL-31 production showed higher symptom and QOL scores during pollen dispersal, and the levels of IL-31 was positively correlated with the scores suggesting that IL-31 is associated with the exacerbation. Th2 cells and ILC2 cells are the major source for type 2 cytokines. ILC2 cells in nasal mucosa are increased in patients with allergic rhinitis, and they produced IL-5 and IL-13 in response to PGD₂ and leukotrienes. In addition, regulatory mechanism for type 2 responses has been clarified in allergen immunotherapy. The immunotherapy can lead to a suppression of type 2 cytokine production and/or an induction of IL-10 via promoting regulatory cells including regulatory T cells and regulatory B cells. In addition, microenvironment especially microbiome in oral cavity affects the efficacy of sublingual immunotherapy.
**ARSR Symposium 3**

**ARSR-S3-2   Keynote Lecture: How to treat allergic rhinitis with sublingual immunotherapy wisely: Experience in korea**

Chae-Seo Rhee

Department of Otorhinolaryngology-Head and Neck Surgery, Seoul National University Hospital, Seoul National University College of Medicine, Seoul, Korea

The prevalence of allergic rhinitis (AR) in the general population is increasing, and prevalence rates are reported to be between 2.9% to 54.1% across various regions and age groups. AR can have a considerable effect on a patient’s quality of life, and can be a cause of substantial socioeconomic burden. Among the current treatment options for AR, specific allergen immunotherapy is the only medical intervention that modifies fundamental immunologic mechanisms by inducing tolerance, and changes the natural course of the disease.

Sublingual immunotherapy (SLIT) for treatment of AR is now widely used, and its efficacy and safety have been established by many clinical trials, studies, and meta-analyses. Studies on the long-term effects of SLIT on AR treatment have shown its efficacy and safety not only in the adult population but also in the pediatric population though the two groups exhibit different levels of immunological factors at baseline. Furthermore, immunologic parameters have been suggested to better predict patient satisfaction with the treatment. However, factors such as new sensitization during SLIT and early adverse events are not correlated with the treatment outcome. As clinicians we should be able to select appropriate patients for SLIT treatment and if necessary, reassure patients to continue with the treatment depending on early parameters.

In this session, I will review about the SLIT with our reported experiences in Seoul National University Hospital, Seoul, Korea, and focus on the changes in immunologic parameters and adverse effects.
Allergic rhinitis is one of the most common health problems globally. The prevalence in Europe ranged from 17% to 28.5%. Whereas, the prevalence in Asia ranged from 6.9% to 30% and tend to increase every year. There are many treatment options for allergic rhinitis symptom control including allergen avoidance and environmental control, various choices of pharmacotherapy; e.g. topical steroids and oral antihistamines, immunotherapy and others; e.g. inferior turbinate reduction, acupuncture and herbal therapy.

Allergen immunotherapy is a repeated allergen administration in order to modulate immune response. Major mechanisms are immune deviation in favor of Th1 deviation and induction of regulatory T cells. Current evidences show that immunotherapy can reduce allergic symptoms, minimize medication usage and prevent new sensitization. Common injectable route of immunotherapy administration is subcutaneous immunotherapy (SCIT) and non-injectable route is sublingual immunotherapy (SLIT). The standardized mean difference of nasal symptom score for SLIT is -0.33[-0.54, -0.13] and for SCIT is -2.17[-3.50, -0.84] as compared to placebo. There is no significant difference for symptom score between SLIT and SCIT. Actually, there are many alternatives of non-injectable immunotherapy such as epicutaneous immunotherapy, intradermal immunotherapy, oral immunotherapy, bronchial immunotherapy, intra-lymphatic immunotherapy and local nasal immunotherapy.

Local nasal immunotherapy (LNIT) is an immunotolerance induction in the nasal cavity. It was first introduced in the 1970s. Nasal dendritic cells in the nasal associated lymphoid tissue (NALT) play an important role for the induction of vaccine-induced priming and disseminating immune response. The network of dendritic cells around nostrils facilitates allergen molecules uptake and initiates the adaptive immune response. This may be the benefit of an immunotolerance induction directly in the nasal cavity which is a shock organ as compare to other non-injectable routes such as SLIT. Evidence demonstrates that LNIT and SCIT provide similar clinical efficacy. Murine model also shows that LNIT is able to induce IL-10 release and desensitization in allergen challenge. LNIT becomes less popular shortly after then because of several reasons; the dosage control difficulty and the compliance matter due to the frequent local side effects and the specific administration techniques needed in order to avoid allergen spillage into lower airway. The most recent randomized controlled trial of LNIT published in 2009.

Non-injectable immunotherapy repossesses attention lately. It is an easy route of administration which can be done by the patient at their home. It is less expensive, less time consuming and less invasive as compare to injection immunotherapy. Moreover, it is less likely to induce systemic reaction. Nasal route could be considered as another option for non-injectable immunotherapy.

---

Curriculum vitae

*Head of Center of Research Excellent in Allergy & Immunology, Faculty of Medicine Siriraj Hospital, Mahidol University, THAILAND.*

Assistant Professor for Research & Academic Affairs, Mahidol University, THAILAND.

Associate Professor Dr. Pongsakorn Tantilipikorn completed his MD degree in 1992, and ENT training in Thailand in 1997. He was a rhinology fellow with Prof David Kennedy in University of Pennsylvania during 1997-1999. From 1999, he worked as an assistant professor in Chiang Mai University till 2004. During 2008-2010, he went to study with Prof Jean Silvain Lacroix at University of Geneva under the topic involved with basic science research in nasal inflammation. He got his PhD of Biostatistic & Epidemiology, under the thesis (with excellent result of defending thesis) title “Nasal Allergy: Diagnostic Criteria and Its Co-morbidities”.

He currently is an Associate Professor and Chief of Center of Research Excellence in Allergy & Immunology of Faculty of Medicine and Assistant President in Research and Academic Affairs, Mahidol University. After being a fellow in American Rhinologic Society and European Rhinologic Society for more than 20 years, he was elected to be a board member of the International Society of Infection and Allergy of the Nose (ISIAN) since 2016. His special interests are: allergen immunotherapy, nasal inflammation, minimally invasive rhinologic procedures, mucosal immunity of nose & paranasal sinuses and pathophysiology of rhinosinusitis.
ARSR Symposium 3

ARSR-S3-4  Local-nasal immunotherapy for allergic rhinitis: A systematic review and meta-analysis

Navarat Kasemsuk, MD*, Premyot Ngatopprutaram, MD†, Dichapong Kanjanawasee, MD, PhD‡, Triphoon Suwanwech, MD*, Stephen R Durham, MD, FRCP§, Giorgio Walter Canonica, MD¶, Pongsakorn Tantilipikorn, MD, PhD

1Division of Rhinology and Allergy, Department of Otorhinolaryngology, Faculty of Medicine Siriraj Hospital, Mahidol University, Bangkok, Thailand
2Allergy and Clinical Immunology, Imperial College London, London, United Kingdom
3Department of Internal Medicine, Respiratory Disease Clinic, IRCCS Humanitas Clinical and Research Center, Humanitas University, Milan, Italy

Rationale: Non-injectable immunotherapy repossesses attention lately. It is an easy route of administration which can be done by the patient at their home, less expensive, less time consuming and less invasive as compare to injection immunotherapy. Moreover, it is less likely to induce systemic reaction. Nasal route could be considered as an appropriate option for non-injectable immunotherapy.

Methods: A systematic search was done using OVID Medline and EMBASE as main databases. We included all RCT comparing LNIT and placebo published in English language, up to 19 December, 2020. Data were pooled for meta-analysis. The heterogeneity measurement and sensitivity analysis were done.

Results: 20 studies with 698 participants were included. The LNIT group had greater post-treatment improvement of TNSS than the control group (SMD -1.37; 95% CI: [-2.04, -0.69]). All the individual symptom scores favour LNIT. SMD and 95%CI of SMS and medication score were -1.55; 95% CI: [-2.83, -0.28] and -1.09; 95% CI: [-1.35, -0.83]. No significant difference for serum specific IgE, nasal IgE and nasal ECP was observed between two groups. Only serum IgG showed significant increase (MD 0.45; 95% CI: [0.20, 0.70]) in LNIT group. The nasal provocation threshold changes obviously favoured LNIT (MD 27.30; 95% CI: [10.13, 44.46]). No significant adverse event was reported.

Conclusion: LNIT improves clinical symptoms, lessen medication usage and increase nasal provocation threshold in allergic rhinitis patients. No severe adverse event for LNIT application was reported. Although there is no difference for serum specific IgE, nasal IgE and nasal ECP, LNIT is still a route of choice for non-injection immunotherapy administration.

ARSR Symposium 3

ARSR-S3-5  Influences of CD8+ Tregs on peripheral blood mononuclear cells from allergic rhinitis patients


Department of Otorhinolaryngology-Head and Neck Surgery, Huashan Hospital of Fudan University, Shanghai, China

Objectives—CD8+(or CD4+) CD25+fork-head box transcription factor (Foxp3)+ regulatory T cells (CD8+ or CD4+ Tregs) all play a significant role in immune homeostasis and tolerance. However, the role of CD8+ Tregs in allergic rhinitis (AR) have not been clearly elucidated. The present study was aimed to assess the influence of CD8+ Tregs on peripheral blood mononuclear cells (PBMCs) from AR patients.

Methods—Patients with AR were enrolled. PBMCs were obtained, and CD4+ and CD8+ Tregs were separated from PBMCs and cultured in vitro. We examined percentages of these Tregs in total CD4+ or CD8+ T cells, respectively. After that, we evaluated levels of interleukin (IL)-10 and transforming growth factor (TGF)-β in Tregs cultures. Finally, we administered CD4+ and CD8+ Tregs from AR patients into PBMCs cultures and examined contents of IL-4 and IL-5.

Results—The percentages of CD4+ or CD8+ Tregs in the total CD4+ or CD8+ T cells from PBMCs in AR patients were reduced compared to normal subjects. However, IL-10 and TGF-β and their mRNAs were increased in CD4+ and CD8+ Tregs cultures from AR patients, and there were no significant differences in their levels between these two Tregs cultures. IL-4 and IL-5 were increased in AR subjects PBMCs compared to normal ones and decreased after the AR CD4+ or CD8+ Tregs administration. However, there were no statistical differences in IL-4 and IL-5 concentrations between these two Tregs treatments.

Conclusions—The findings demonstrate that CD8+ Tregs may alleviate inflammatory responses in AR condition.

Keywords
CD4+ Tregs; CD8+ Tregs; allergic rhinitis; PBMCs
ARSR Symposium 3

ARSR-S3-6  Endoscopic sinus surgery for olfactory dysfunction caused by eosinophilic chronic rhinosinusitis

Masayoshi Kobayashi*, Kazuhiko Takeuchi

Otorhinolaryngology-Head and Neck Surgery, Mie University Graduate School of Medicine, Tsu, Japan

I. Introduction

Eosinophilic chronic rhinosinusitis (ECRS) is a refractory disease and induces conductive olfactory dysfunction in most cases. An endoscopic sinus surgery (ESS) is often applied to cases in which treatment with steroid is not so effective or steroid is difficult to use for its side effects. Critical points of the ESS for improving olfactory dysfunction are to restore airflow of the olfactory cleft and superior meatus of nose and to open the ethmoidal sinus. However, inappropriate operation in olfactory cleft may cause mucosal adhesion and idiopathic olfactory loss. Therefore, delicate and careful manipulation is required. Here we show how to perform ESS for ECRS to improve olfactory dysfunction.

II. Methodology

For ECRS cases, full-house ESS is applied to make sinonasal airflow condition better. Since olfactory cleft is narrow and its mucosa bleeds easily, suctioning tools as suction curette and microdebrider are helpful to get clear surgical view and remove polyps in the olfactory cleft. If many polyps occupied the olfactory cleft and wounded surface is wide after removing polyps, we insert gelatin sponge into the olfactory cleft and inject steroid solution into the sponge to prevent mucosal adhesion and scar formation.

III. Results

In the ESS cases, 81% of the cases could restore their olfactory function after the surgery. In the cases applied the gelatin sponge-steroid method, 86% of the cases could restore their olfactory function after the ESS.

IV. Conclusion

ESS is useful to restore olfactory function caused by refractory ECRS when using appropriate surgical techniques.