



Sublingual Immunotherapy in Allergic Rhinitis: Search for a Suitable Biomarker Continues!

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Allergic rhinitis (AR) in children is a common problem that has increased over past several decades and is frequently associated with asthma. It is due to dysregulation of immune system causing increase in inflammation and formation of specific IgE antibodies against several otherwise harmless environmental allergen/s. Among various allergens, house dust mite seems to be most common allergen for allergic rhinitis in children. Symptomatic treatment with antihistaminics (oral or nasal) and/or nasal corticosteroids is sufficient in majority of cases of AR in children. A subset of children with severe AR not responding to this conventional therapy may be benefitted by allergen-specific immunotherapy (AIT) by subcutaneous (SCIT) or sublingual (SLIT) route, the latter being increasingly used recently [1]. The guidelines have been developed for effective use of AIT in children [2].

The mechanism that leads immune tolerance in allergic rhinitis by SCIT/SLIT is complex and poorly understood till yet and researchers are trying to identify the exact mechanism. AIT corrects the immunological imbalance by shifting cytokine pattern from Th2 (IL-4, IL-5, IL-13) to Th1 type. Further, AIT reduces allergen specific IgE production, induces IgG4 blocking antibodies and promotes Treg cells that result in allergen tolerance. However, there is a lack of reliable biomarker that can be used for selecting the patient for AIT and monitoring the treatment response. Interleukin-33 (IL-33), a member of IL-1 family, is an important part of T helper 2 (Th2) immune response that upregulates in allergic conditions including allergic rhinitis [3]. Levels of IL-33 have been correlated with severity of allergic rhinitis [4]. The IL-13 is being explored as a potential biomarker for response and monitoring of AIT in allergic rhinitis.

A study by Wang et al. [5] published in this issue adds to role of IL-33 in immunotherapy. Authors enrolled sixty children with AR for this case controlled prospective study. Thirty children out of these sixty children received house dust mite (HDM) allergen extract for SLIT and rest were in placebo group for 2 y. Authors found significant decline in IL-33 levels in serum and nasal lavage after 12 mo and 24 mo of SLIT treatment and reduced nasal IL-33 levels were associated with increased nasal IL-10 (a Treg cytokine) at 2 y of therapy. They also reported an in vitro test where IL-33 enhanced Th1 response (increased IL-4 and IL-5) and inhibited Th2 response (decreased IL-10) in peripheral blood mononuclear cells in allergic rhinitis [5]. Though, it is a part of multicenter study and results of whole study will provide more insights into SLIT in children with allergic rhinitis. ST2 is a receptor for IL-33 and in another recent study, ST2 + CD45RO + CD4+ cells were increased in peripheral blood in adult patients of AR exposed to HDM and were significantly decreased after 1 y of SLIT therapy with HDM allergen [6]. A study by Nasr et al. showed that patients with AR had significantly higher levels of IgE and IL-33 in comparison to control group and level of IL-33 declined significantly along with clinical improvement [7].

The duration of SLIT is not well defined and it is used for 2–3 y, but data are not robust for long lasting effects (both clinical and biochemical) of SLIT after stopping the therapy. The assessment of cytokine levels after cessation of treatment on follow-up in index study would have given sustainability of SLIT for allergic rhinitis. Though SLIT is effective and not having major side-effects, the duration of SLIT is usually for 2–3 y and symptoms of AR may be for approximately 3 mo in a year. The daily therapy for 3 y for relief of 3 mo symptoms may not be acceptable to all.

Children with AR usually have allergy to more than one allergen and it would be a millionaire question whether using SLIT for one allergen might be effective for other allergy also. If so, how to decide best allergen for SLIT in polysensitized children, will be the next task. This aspect was not studied in

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the index study. Though there are studies [8] suggesting efficacy of single allergen SLIT in both monosensitized and polysensitized children, more studies are required to establish the mechanism and efficacy of single allergen SLIT for polysensitized children.

Finally, SLIT may not be effective for all. It will be interesting to know the factors associated with success or failure of SLIT. Gotoh et al. [9] did a study to identify a biomarker to predict a response to SLIT against pollen induced AR and found that no single biomarker differentiated the responders from non-responders, but analysis of pre-therapy serum parameters with the Adaptive Boosting (AdaBoost) algorithm and cluster analysis was able to differentiate responders from non-responders [9].

To summarize, there is still a need to identify a biomarker that can be used to start the therapy, to predict the response and finally to monitor the response after SLIT. The IL-33 could be such a marker but requires more studies in large number of population before making any recommendations for SLIT for children with AR.

Compliance with Ethical Standards

Conflict of Interest None.

References

1. Zielen S, Devillier P, Heinrich J, Richter H, Wahn U. Sublingual immunotherapy provides long-term relief in allergic rhinitis and reduces the risk of asthma: a retrospective, real-world database analysis. *Allergy*. 2018;73:165–77.
2. Pajno GB, Bernardini R, Peroni D, et al. Clinical practice recommendations for allergen-specific immunotherapy in children: the Italian consensus report. *Ital J Pediatr*. 2017;43:13.
3. Rogala B, Glück J. The role of interleukin-33 in rhinitis. *Curr Allergy Asthma Rep*. 2013;13:196–202.
4. Glück J, Rymarczyk B, Rogala B. Serum IL-33 but not ST2 level is elevated in intermittent allergic rhinitis and is a marker of the disease severity. *Inflamm Res*. 2012;61:547–50.
5. Wang Y, Li C, Xu Y, et al. Sublingual immunotherapy decreases expression of interleukin-33 in children with allergic rhinitis. *Indian J Pediatr*. 2018. <https://doi.org/10.1007/s12098-018-2703-3>.
6. Ihara F, Sakurai D, Yonekura S, et al. Identification of specifically reduced Th2 cell subsets in allergic rhinitis patients after sublingual immunotherapy. *Allergy*. 2018. <https://doi.org/10.1111/all.13436>.
7. Nasr WF, Sorour SS, El Bahrawy AT, Boghdadi GS, El Shahaway AA. The role of the level of interleukin-33 in the therapeutic outcomes of immunotherapy in patients with allergic rhinitis. *Int Arch Otorhinolaryngol*. 2018;22:152–6.
8. Wang Z-x, Shi H. Single-allergen sublingual immunotherapy versus multi-allergen subcutaneous immunotherapy for children with allergic rhinitis. *J Huazhong Univ Sci Technol*. 2017;37:407–11.
9. Gotoh M, Kaminuma O, Nakaya A, et al. Identification of biomarker sets for predicting the efficacy of sublingual immunotherapy against pollen-induced allergic rhinitis. *Int Immunol*. 2017;29:291–300.