

ORIGINAL ARTICLE

ARTICOLO ORIGINALE

Sublingual immunotherapy-induced IL-10 production is associated with improvement of nasal airflow resistance: preliminary report

La produzione di IL-10 indotta dall'immunoterapia sublinguale è associata ad un miglioramento delle resistenze nasali: studio preliminare

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Key words

Allergic rhinitis • Nasal obstruction • Nasal airflow resistance • Rhinomanometry • Sublingual immunotherapy • IL-10

Parole chiave

Rinite Allergica • Ostruzione Nasale • Resistenze Nasali • Rinomanometria • Immunoterapia sublinguale • IL-10

Summary

Background

Sublingual immunotherapy has been demonstrated to be able of inducing a regulatory T cell (Treg) response as evidenced by IL-10 production. Nasal obstruction may be measured by rhinomanometry.

Objective

The aim of this study was to assess the association of sublingual immunotherapy-induced IL-10 production with nasal airflow resistances.

Methods

19 patients with perennial allergic rhinitis were studied: 9 successfully assumed sublingual immunotherapy for 3 years, 10 were considered as control. In vitro IL-10 production was evaluated after sublingual immunotherapy. Rhinomanometry was performed in all subjects before and after 3 years.

Results

After 3 years, sublingual immunotherapy-patients showed a significant decrease of nasal resistances (0.048). The comparison with non-treated allergic patients shows significant differences ($p = 0.02$). In addition, the percentages of reversibility were associated with IL-10 levels ($p = 0.0016$).

Conclusions

This study provides the first evidence of an association between improved nasal resistances and Treg-induced IL-10 production after sublingual immunotherapy in patients with perennial allergic rhinitis.

Premesse

È stato dimostrato che l'immunoterapia sublinguale è in grado di indurre una risposta delle cellule T regolatorie come evidenziato dalla produzione di IL-10.

Scopo dello studio è stato la valutazione dell'associazione tra la produzione di IL-10 indotta dall'immunoterapia sublinguale e le resistenze nasali.

Metodi

Erano studiati 19 pazienti con rinite allergica perenne: 9 avevano assunto con successo l'immunoterapia sublinguale per 3 anni, 10 erano considerati come controllo. Veniva valutata in vitro la produzione di IL-10 dopo la terapia. Una rinomanometria era eseguita prima e dopo la terapia.

Risultati

Dopo 3 anni, i pazienti trattati con immunoterapia presentavano un significativo decremento delle resistenze nasali (0,048). Tale effetto era significativamente differente rispetto ai soggetti non trattati (0,02). Inoltre, la percentuale di reversibilità era associata con i livelli di IL-10 (0,0016).

Conclusioni

Questo studio dimostra in maniera evidente l'esistenza di un'associazione tra il miglioramento della funzionalità nasale e la produzione di IL-10 indotta dall'immunoterapia sublinguale in pazienti con rinite allergica perenne.

Nasal obstruction is a key symptom in patients with allergic rhinitis¹ and is related to allergic inflammation². In this regard, a relationship among nasal obstruction symptom, Th2-dependent inflammation, and airflow limitation has been demonstrated in patients suffering from allergic rhinitis². Moreover, this symptom may be objectively measured by rhinomanometry³.

Allergic disorders are characterized by a defect of regulatory T cells (Treg), a family of T-cell subsets that release IL-10 and TGF β ⁴. Specific immunotherapy is able of inducing IL-10 production, thus filling the Treg defect⁵. Very recently, it has been reported that also sublingual immunotherapy (SLIT) induces IL-10 production which is associated with clinical improvement in patients with perennial allergic rhinitis⁶. Moreover, SLIT reduces T cell proliferation⁷. These immunological changes are related with the induction of allergen-specific tolerance: the main mechanism that explains the clinical improvement.

This study aimed at evaluating nasal airflow resistances and IL-10 production in SLIT-treated patients.

Nine patients suffering from perennial allergic rhinitis (PAR) undergoing SLIT had received mite aller-

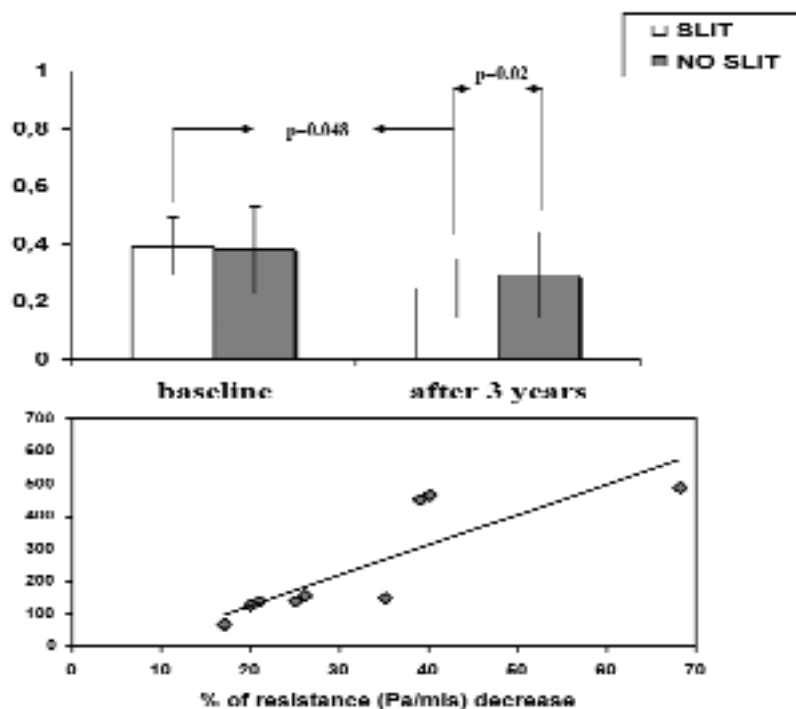
gen extract (Staloral 100 IR, Stallergenes, Milan, Italy) for 3 years; 10 PAR patients non treated with SIT were considered as control. Demographic and clinical characteristic have been previously reported^{6,7}. Patients were clinically evaluated at baseline, i.e. before SLIT, and after 3 years.

Active anterior rhinomanometry was performed as previously reported¹². IL-10 production was stimulated by *Dermatophagoides farinae* or *Candida albicans*^{6,7}. The quantitative determination of *in vitro* production of IL-10 was performed by a commercial ELISA (Pantec s.r.l., Turin, Italy). The statistical analysis was performed using the non-parametric Mann-Whitney *U* test, the Spearman test, and the ANOVA test.

Nasal symptoms significantly improved after SLIT ($p < 0.01$). IL-10 production was detectable only in SLIT-treated patients in comparison with allergic non-treated patients: *Candida*-induced IL-10 158 pg/mL (141-453) vs. 0 (0-0) ($p = 0.002$); *Dermatophagoides farinae*-induced 80 pg/mL (0-113) vs. 0 (0-0) ($p = 0.04$).

At baseline, mean nasal airflow resistances were: 0.39 ± 0.17 (Pa/mL/s) in SLIT-group and 0.38 ± 0.22 in control group, without statistical difference

Fig. 1. Upper panel: nasal airflow resistances (expressed as Pa/mL/sec) evaluated before and after 3 years in patients treated or not-treated with SLIT. Data are expressed as means $\pm$ SD.



Lower panel: IL-10 levels and decrease of resistance (expressed as %) in SLIT-treated patients after 3 years.

between the two groups ($p = 0.995$), as reported in Figure 1.

After three years, nasal airflow resistances significantly decreased in SLIT-treated patients (0.247 ± 0.04 ; $p = 0.048$), whereas did not significantly change in control group (0.337 ± 0.09 ; $p = 0.788$). The intergroup analysis shows a statistical significant difference ($p = 0.02$).

In addition, the most important finding of this study is that the decrease of nasal airflow resistance values is significantly associated with IL-10 production ($p = 0.0016$).

Nasal airflow resistances may be considered a reliable marker of nasal obstruction in patients with allergic rhinitis^{2,3}. Moreover, successfully specific immunotherapy has been demonstrated capable of inducing IL-10 production by Tregs⁵. IL-10 exerts a number of documented activities that are relevant for understanding the mechanisms of action of SIT: the modulation of allergen-specific IgE production in favour of IgG4, the inhibition of allergen-dependent mast cell activation, the suppression of activation and survival of eosinophils, the reduction of

pro-allergic cytokines, and the hyporeactivity to allergens such as the induction of specific tolerance⁵.

SLIT is a safe and effective route of administration of allergen extracts in allergic patients. However, its mechanism of action is still poorly understood, as there are few data concerning the induced immunological changes. We previously provided evidence that SLIT was able of inducing a Treg-dependent response that was related with the observed clinical and immunological changes^{6,7}.

This study provides additional evidence that SLIT improves the rhinomanometric impairment in patients with PAR as documented by the decreased nasal airflow resistance values.

Moreover, the most important finding of this study is the evidence that the IL-10 levels are associated with the nasal resistance improvement.

In conclusion, this pilot study shows that SLIT is able of improving nasal obstruction in patients with PAR and this functional effect is dependent on immunological changes, such as the induction of a Treg response.

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