



Letter to the Editor

Impairment of lung function might be related to IL-10 and IFN- γ defective production in allergic children[☆]

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ABSTRACT

A functional defect of T regulatory cells (Tregs) has been proposed as pathogenic mechanism of allergic reaction. Impairment of lung function frequently occurs in children with respiratory allergy. This study aimed at investigating the possible role of IL-10 and IFN- γ on lung function deterioration in allergic children. Forty children with mild asthma, monosensitized to house dust mites, were evaluated and followed-up for 2 years. Spirometry was performed in all children. IL-10 and IFN- γ were evaluated in *in vitro* experiments. FEV₁, FVC, and FEF_{25–75}, evaluated as percent of predicted, significantly diminished over time ($p < 0.0001$, $p = 0.03$, and $p < 0.0001$ respectively). There was a strong relationship between changes in spirometric parameters and IL-10 production and between changes in FEV₁ values and IFN- γ production over time.

This preliminary study provided evidence that IL-10 and IFN- γ production could be defective in allergic children prone to develop functional impairment.

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An allergen-specific functional defect of T regulatory cells (Tregs) may promote Th2 polarization and IgE synthesis in allergic patients [1–4]. Th2 polarization is characterized by increase of Th2-dependent cytokines production and conversely reduced release of Th1-dependent cytokines. Tregs are capable to produce a variety of cytokines, including IL10 and TGF- β , whereas IFN- γ is mainly produced by Th1 cells [2].

The natural history of allergy is frequently characterized by a progressive worsening of the clinical manifestations, with involvement of additional target organs (e.g. from rhinitis to asthma), increased symptom severity, and functional deterioration: the so called “allergic march” [5–8]. In addition, a tendency to become sensitized to other allergen classes in children monosensitized has been described [9]. Interestingly, it has been recently suggested that IL-10 and IFN- γ production could be defective in allergic children prone to develop poly-sensitisation [8]. As the natural history of allergic asthma in childhood is characterized by worsening of the pulmonary function in a significant proportion of individuals [10], a relationship between the functional changes and the immunological background may be hypothesized.

The present preliminary study was therefore designed to investigate the possible role of two cytokines, IL-10 and IFN- γ , in the development of progressive lung function deterioration in children with allergic asthma.

Forty allergic children (24 males and 16 females, mean age 7.2 years), monosensitized to house dust mites (HDM), with mild intermittent asthma were progressively recruited from a population

referred to our outpatient clinic. Allergy and asthma were diagnosed according to validated criteria [5,8,11].

At enrolment, asthmatic children had to be inhaled or systemic corticosteroid-free and not treated with allergen-specific immunotherapy. The Institutional Ethical Committee of the G. Gaslini Institute approved the protocol. Signed informed parental consent was obtained. Children were followed every 6 months for 2 years. At entry and at the end of the study period, clinical assessment, including pulmonary function measurements, were performed every 6 months. Forced vital capacity (FVC), forced expiratory volume in 1 second (FEV₁), and forced expiratory flow between 25 and 75% of vital capacity (FEF_{25–75}) were expressed as predicted values. Total IgE serum levels were measured at baseline and after 24 months. Randomly, IFN- γ and IL-10 production by peripheral blood mononuclear cells (PBMC) was also evaluated in 8 children, at beginning and at the end of the study period. Methods have been previously described [8]. The statistical package “Statistica” (StatSoft Corp., Tulsa, OK) was used for all the analyses.

In the whole study population, a tendency to a decrease in pulmonary flows and volumes was detected in the 24 month follow-up period (Fig. 1A–C). Specifically, as compared with the baseline assessment, FVC values significantly diminished only over time ($p = 0.03$), whereas the decrease in FEV₁ and FEF_{25–75} values was already significant at 12- and 18-months. Total serum IgE levels significantly increased over time being 212 (109.640) kU/l [median (lower–upper quartiles)] at baseline and 302 (172–777) kU/l at 24 months ($p = 0.013$).

In the 8 children in whom cytokine production by PBMC was evaluated, a tendency to a progressive decrease in PHA-induced IL-10 and IFN- γ release was observed from baseline to final values. In details, IL-10 concentrations in PHA-stimulated PMNCs cultures were 20.72 (9.27–33.43) at baseline and 17.34 (9.74–23.57) ng/ml

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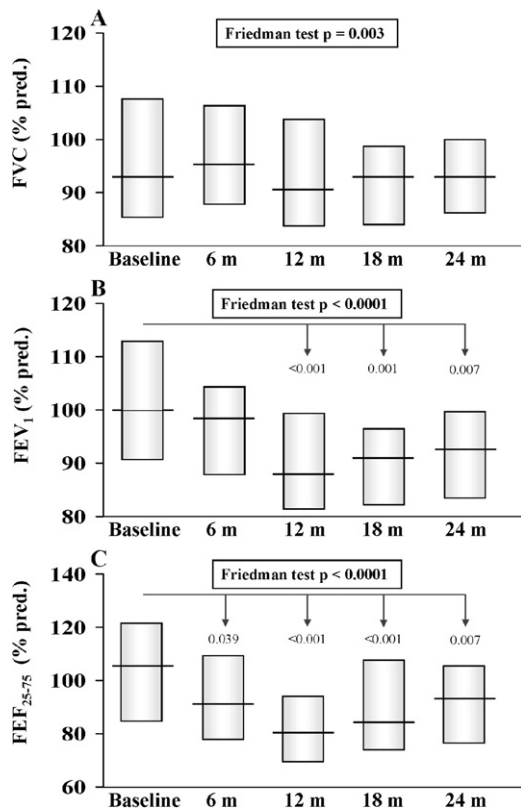


Fig. 1. Changes in FEV₁, FEF₂₅₋₇₅ and FVC values during the 24 month follow-up period. Data are expressed as medians; bars represent first and third percentiles.

at 24 months, while IFN- γ concentrations were 560.0 (406.6–734.8) and 325.1 (262.1–518.0) ng/ml, respectively. However, the differences between “baseline” and “24-month” concentrations did not reach the statistical significance for both IL-10 and IFN- γ ($p = \text{NS}$).

Interestingly, despite the low number of children evaluated, strong positive correlations were observed between changes in all pulmonary function parameters evaluated (FEV₁, FEF₂₅₋₇₅ and FVC) and modifications in PHA-induced IL-10 release over time (respectively: $r = 0.762$, 0.738 , and 0.762) (Fig. 2A–C). In contrast, the decrease in PHA-induced IFN- γ release significantly correlated only with FEV₁ changes ($r = 0.738$) (Fig. 2D). No correlations were observed between total IgE and FVC, FEV₁ and FEF₂₅₋₇₅ over time, both in the whole population and in the 8 children in whom cytokine production by PBMC was evaluated.

Therefore, this preliminary study may provide some interesting findings:

- allergic children with mild asthma may show a tendency to develop pulmonary function deterioration in a very short period of time, such as two years [7], non associated with the slight modifications in total serum IgE levels;
- PBMCs from a little subgroup of these allergic children with mild asthma tended to progressively secrete lower levels of IFN- γ and IL-10 (following stimulation with PHA), in the two-year follow-up;
- there were strong relationships between spirometric changes and cytokine production modifications over the observation period.

The observed lack of correlation between pulmonary function values and total IgE (surrogate markers of Th2-dependent

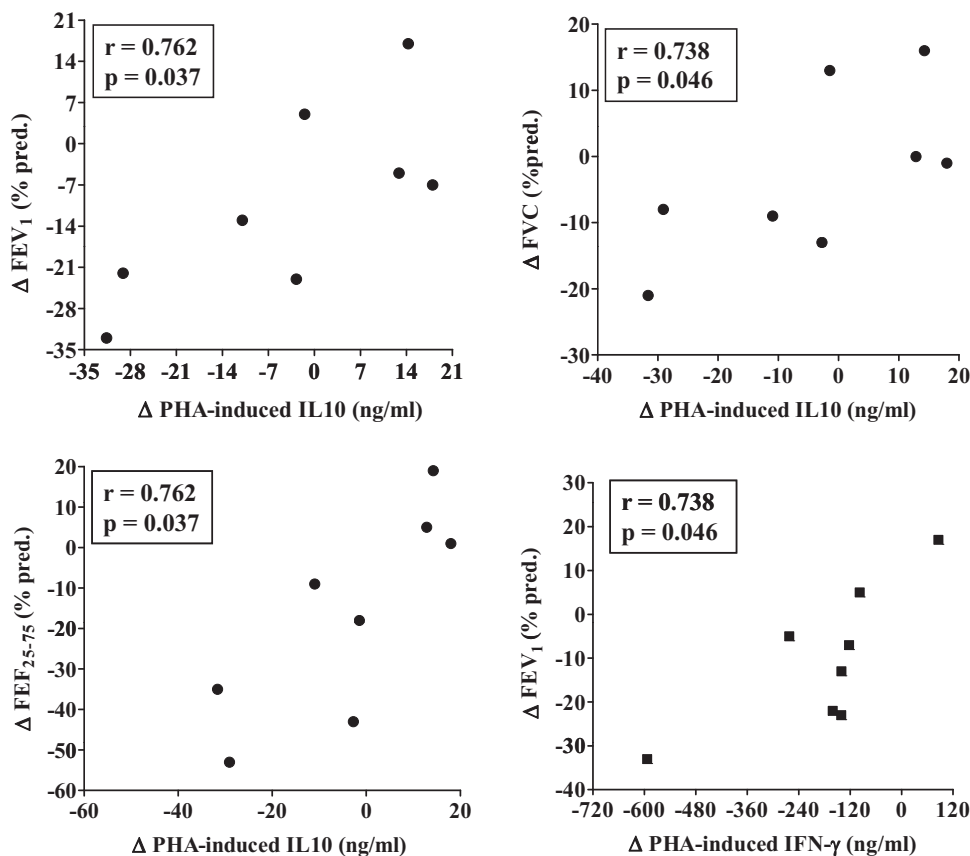


Fig. 2. Correlations between the changes in PHA-induced cytokine release (A–C: IL-10 and D: IFN- γ) and modification in pulmonary function parameters (FEV₁, FEF₂₅₋₇₅ and FVC).

immune response) is not surprising, since the same observation has been previously reported in a similar group of children [12]. On the contrary, interesting are the preliminary data supporting the hypothesis that the development of pulmonary function deterioration might be associated with a defective production of some cytokines, such as of IFN- γ and IL-10, involved in allergic response [3,4]. Possible source of these cytokines could be impaired Tregs, as there are some sub-sets able of producing also IFN- γ or Th1 cells, as decreased Th1 may promote the typical allergic shift to Th2 responses. However, this study did not consider the phenotypic analysis of cells producing these cytokines. As both IL-10 and IFN- γ can be produced by different sub-populations present in PBMC, the exact source of these cytokines cannot be defined. In addition, other limitations of this study are the low number of children evaluated and the short observation-time.

In conclusion, this preliminary study shows that allergic children with asthma may have a respiratory function decline which might depend on immunological changes. Further studies should be conducted on a larger cohort of allergic children with a longer follow-up period, to corroborate this hypothesis.

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