



Letter

Improvement in lung function is associated with a decrease in serum soluble CD30 in atopic infants

Only a minority of infants with recurrent or prolonged respiratory symptoms will develop asthma. The development of asthma is speculated to be associated with T-helper cell type 1 (T_H1) and type 2 (T_H2) lymphocyte activity imbalance, because an inappropriate T_H2 response causes pulmonary inflammation, airway eosinophilia, and airway hyperresponsiveness to various stimuli. In addition, in asthmatic inflammation, T_H1 cells can contribute to T_H2-type reactions by promoting T-cell migration to the airways and by enhancing T-cell–dependent IgE production in the airways.

CD26 and CD30 are membrane molecules expressed on activated lymphocytes. CD26 is a multifunctional surface glycoprotein responsible for the degradation of interferon- γ –induced chemokines, and it is highly expressed on activated T_H1 cells. CD30 is a glycoprotein that belongs to the tumor necrosis factor receptor family, and its expression is upregulated and sustained especially in activated T_H2 cells. At T-cell activation, the soluble forms of these surface glycoproteins, sCD26 and sCD30, are released by proteolytic cleavage to the blood stream.

Elevated levels of sCD26 in plasma have been found in patients with atopic dermatitis and allergic asthma.^{1,2} In contrast, sCD26 has been found to be inversely associated with disease severity in patients with chronic eosinophilic pneumonia.³

Increased levels of sCD30 in serum samples have been found in patients with atopic dermatitis,⁴ and an association between elevated sCD30 and the severity of eczema has been observed.⁴ In addition, increased levels of serum sCD30 have been seen in patients with allergic asthma.^{4–6} However, there are few reports on the role of sCD30 in activity of asthma⁴ or on the effect of intervention on sCD30 levels.⁵ Soluble CD26 and sCD30 are age dependent, with serum levels of sCD26 increasing until adolescence and sCD30 decreasing throughout childhood.⁷ These factors should be taken into account when evaluating the potential clinical utility of these markers.

In our previous study, we found that budesonide therapy for 6 weeks improved lung function in infants with troublesome lung symptoms, especially in those with atopy.⁸ The purpose of the present study was to clarify whether serum sCD26 and sCD30 levels are linked to lung function changes and atopy in the same cohort.

The study subjects included 43 infants (median 12.4 months old, range 3.7 to 25.9 months old) with persistent cough, recurrent wheeze, or shortness of breath who were randomized to receive budesonide or placebo for 6 weeks, as described previously in

detail.⁸ Before the intervention, the children were examined clinically, and whole body plethysmography was performed.⁸ In addition, serum samples were obtained for the determination of serum sCD26 and sCD30, as described previously.⁶

The study was approved by the research ethics committee of the regional university hospital. Before participation in the study, written informed consent was obtained from the parents of all children in the study.

To evaluate statistical differences between groups, the χ^2 test or Fisher exact test was used for dichotomous variables, and the Kruskal-Wallis or Mann-Whitney *U* test was used to analyze continuous variables. Correlations between continuous and/or ordinal variables were determined using the Spearman rank correlation test. The Wilcoxon signed ranks test was used to analyze the difference between repeated measurements. Two-tailed tests were used in all analyses. *P* values less than .05 were considered statistically significant. Data were analyzed using IBM SPSS 19.0 for Windows (IBM, Armonk, New York).

Baseline levels of serum sCD26 and sCD30 were within the normal limits determined for 1- to 2-year-old children⁷ in most children (98% and 70%, respectively). At baseline, serum sCD26 and sCD30 levels did not differ between the intervention groups, and there were no differences in baseline data, including age, sex, atopic traits, clinical findings, or whole body plethysmographic measurements, between the 2 intervention groups.⁸

Serum sCD26 or sCD30 levels did not correlate with age or baseline lung function, but there was a significant negative correlation between serum sCD26 and sCD30 ($P = .038$, $r_s = -0.318$). In addition, children with atopy (positive skin prick test reaction and/or having atopic eczema, $n = 22$) tended to have higher levels of serum sCD30 than those without atopy ($n = 21$, $P = .050$).

A general increase was seen between the sCD26 levels measured before and after the 6-week intervention ($P = .012$), but the increase was independent of atopy and intervention. In contrast, serum sCD30 levels tended to decrease during the 6-week intervention ($P = .025$). The median decrease in serum sCD30 was greatest in children with atopy treated with budesonide (-53.1 IU/mL), whereas in children with atopy treated with placebo and those without atopy treated with budesonide or placebo, the respective changes were -0.5 , $+16.2$, and -19.2 IU/mL ($P = .023$). Moreover, there was a significant correlation between the increase in specific conductance and the decrease in serum sCD30 levels in children with atopy (Fig 1). However, such a correlation was not seen in children without atopy.

These results support the previous findings on sCD30 as a possible marker of atopy. Conversely, serum levels of sCD26 could not be shown to be associated with atopy or lung function, in

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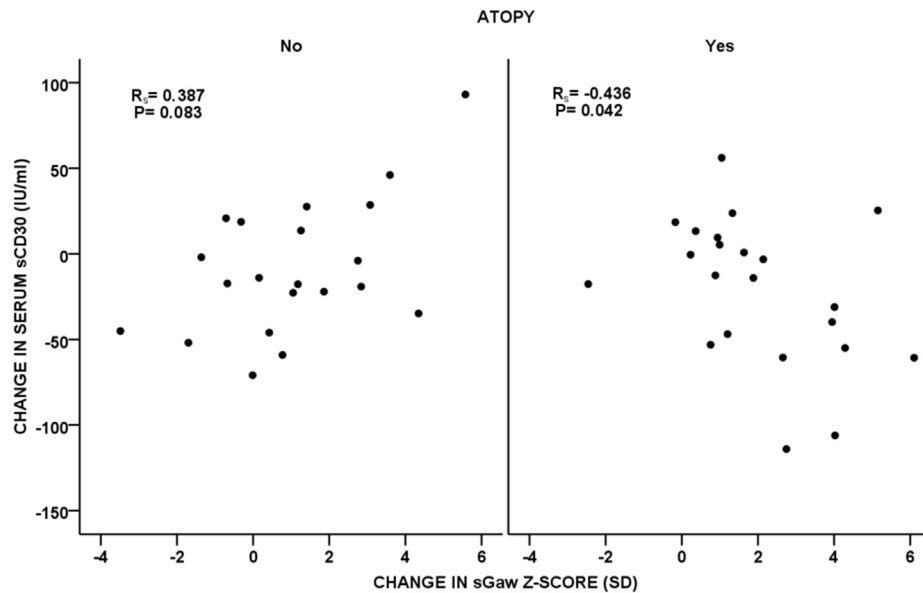


Figure 1. Changes in serum soluble CD30 (sCD30) and specific conductance (sGaw) with regard to atopy.

accordance with a previous report.⁶ The expression of high levels of CD30 has been found to induce activation of a proinflammatory transcription factor, nuclear factor- κ B, resulting in enhancement of inflammation.⁹ Conversely, corticosteroids suppress inflammation by inhibiting the action of nuclear factor- κ B.¹⁰ Consistent with that, and in line with previous intervention studies,^{1,5} the decrease in serum sCD30 seen in our study was linked to the concurrent improvement of lung function, especially in children with atopy who received inhaled budesonide.

Our report is the first to show that the improvement of lung function was associated with a decrease in serum sCD30 in young children with atopy and troublesome lung symptoms. More studies are needed to clarify whether sCD30 will be suitable as a biomarker for therapy response.

In conclusion, levels of serum sCD30 tend to be higher in individuals with atopy. Improvement in lung function seems to be associated with a decrease in sCD30 in children with atopy and troublesome lung symptoms. The results imply that there are peripheral blood biomarkers that might reflect changes in underlying asthmatic inflammation.

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References

- [1] Katoh N, Hirano S, Suehiro M, et al. Soluble CD30 is more relevant to disease activity of atopic dermatitis than soluble CD26. *Clin Exp Immunol*. 2000;121:187–192.
- [2] Lun SWM, Wong CK, Ko FWS, Hui DSC, Lam CWK. Increased expression of plasma and DC4+ T lymphocyte costimulatory molecule CD26 in adult patients with allergic asthma. *J Clin Immunol*. 2007;27:430–437.
- [3] Matsuno O, Miyazaki E, Nureki S, Ueno T, Ando M, Kumamoto T. Soluble CD26 is inversely associated with disease severity in patients with chronic eosinophilic pneumonia. *Biomark Insights*. 2006;1:201–204.
- [4] Heshmat NM, El-Hadidi ES. Soluble CD30 serum levels in atopic dermatitis and bronchial asthma and its relationship with disease severity in pediatric age. *Pediatr Allergy Immunol*. 2006;17:297–303.
- [5] Purrelo-D'Ambrosio F, Gangemi S, Ruella G, Marotta G, Merendino RA. Effect of fluticasone propionate on soluble CD30 release in patients with severe allergic asthma. *J Invest Allergol Clin Immunol*. 2000;10:283–285.
- [6] Remes ST, Delezuch W, Pulkki K, Pekkanen J, Korppi M, Matinlauri IH. Association of serum-soluble CD26 and CD30 levels with asthma, lung function and bronchial hyper-responsiveness at school age. *Acta Paediatr*. 2011;100:e106–e111.
- [7] Delezuch W, Marttinen P, Kokki H, et al. Serum and CSF soluble CD26 and CD30 concentrations in healthy pediatric surgical outpatients. *Tissue Antigens*. 2012;80:368–375.
- [8] Pelkonen AS, Malmström K, Malmberg LP, et al. Budesonide improves decreased airway conductance in infants with respiratory symptoms. *Arch Dis Child*. 2009;94:536–541.
- [9] Abdulamir AS, Kadhim HS, Hafidh RR, et al. Severity of asthma: the role of CD25⁺, CD30⁺, NF- κ B, and apoptotic markers. *J Invest Allergol Clin Immunol*. 2009;19:218–224.
- [10] Barnes PJ. Corticosteroid effects on cell signalling. *Eur Respir J*. 2006;27:413–426.