Serum soluble T-H cell activity markers and high-sensitivity C-reactive protein in multiple-trigger wheezers

Kotaniemi-Syrjänen, Anne

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Serum soluble T<sub>H</sub> cell activity markers and high-sensitivity C-reactive protein in multiple-trigger wheezers

Deviation of immune responses toward T<sub>H</sub>2 cell reactions results in eosinophilic inflammation of the mucosa and increased responsiveness to various stimuli in the respiratory tract. Such T<sub>H</sub>2-type inflammation has been found in endobronchial biopsy specimens in children with multitrigger wheeze and reduced lung function and might be detected as low-grade systemic inflammation. On the other hand, T<sub>H</sub> cells other than T<sub>H</sub>2-lymphocytes may contribute to eosinophilic inflammation of the airways.

Traditionally, in practices other than those of tertiary care, assessment of airways inflammation in wheezy preschool children has been based on clinical measures. During recent years, peripheral blood biomarkers, which reflect the activation of T<sub>H</sub>1 cells, have been recognized. Serum soluble CD30 (sCD30), a marker of T<sub>H</sub>1-cell activation, has been associated with asthma and lung function<sup>2,3</sup> and evaluated as a potential therapy response marker.<sup>2,3</sup> The role of serum soluble CD26 (sCD26), reflecting T<sub>H</sub>1 cell activity, seems to be more equivocal in the pathogenesis of asthma.<sup>2,3</sup> To date, there are no reports on the association of these T<sub>H</sub>1 cell activity markers and the presence of low-grade systemic inflammation.

In our prior study, 105 children with multiple-trigger wheeze and evidence of bronchodilator responsiveness and/or exercise-induced bronchoconstriction were randomized to receive inhaled fluticasone propionate, 100 µg twice daily, inhaled salmeterol and fluticasone propionate combination, 50/100 µg twice daily, or inhaled salmeterol, 50 µg twice daily for 8 weeks.<sup>1</sup> As a result of the intervention, exhaled nitric oxide fraction (FeNO) decreased and lung function was improved more in the fluticasone and salmeterol-fluticasone groups than in the salmeterol group.<sup>1</sup> Moreover, lung function improved slightly more in the salmeterol-fluticasone group when compared with the fluticasone group.<sup>1</sup> On this basis of this, we hypothesized that pulmonary function abnormalities observed in the cohort could be related to imbalance in activation of different T<sub>H</sub>1 cell populations and might be tracked by peripheral blood biomarkers.

Concentrations of sCD26 and sCD30 were determined from serum samples obtained at baseline and after the intervention, using the enzyme-linked immunosorbent assay method.<sup>7</sup> The intra-assay precisions were 8% and 6% and the interassay precisions were 15% and 14% for serum sCD26 and sCD30, respectively.<sup>7</sup> Age- and sex-adjusted reference values were applied to define abnormal serum sCD26 and sCD30 levels.<sup>2</sup> Interleukins 4, 10, and 13 were measured at baseline and after the intervention using the LINCoplex assay (Lincos Research Inc, St Charles, Missouri) and the LumineX R 100 TM instrument (Luminex Corp, Austin, Texas).<sup>1</sup> Serum high-sensitivity C-reactive protein (hs-CRP) was measured at baseline using the immunoturbidimetric assay (CRPHS, Roche Diagnostics GmbH, Mannheim, Germany). The serum hs-CRP level was considered elevated when the concentration was at the 75 percentile or over of the age- and sex-specific percentiles.<sup>1</sup>

Fifteen of the original cohort of 105 children were excluded from the final analyses because of inadequate serum samples for sCD26 and sCD30 determination. In addition, 3 children were excluded from hs-CRP analyses because CRP-level was 10 mg/L or greater.<sup>1</sup> The study was approved by the Research Ethics Committee of the regional university hospital. Before participation of the study, written informed consent was obtained from parents of all study children.

The statistical tests were chosen depending on whether the data were normally distributed or not. If applicable, the data were log transformed before analyses. Correlation was evaluated by Pearson or Spearman rank correlation tests or the Kendall <i>τ</i> statistic. To adjust for age in correlation analyses, analysis of covariance was performed. Differences between groups were analyzed by the <i>χ</i><sup>2</sup> or Fisher exact test, <i>t</i> test, Mann-Whitney <i>U</i> test, analysis of variance, or Kruskal-Wallis test. In repeated measurements, the <i>t</i> test for paired samples or the Wilcoxon signed rank test was performed. To compare repeated measurements between the intervention groups, general linear model for repeated measures was applied.

At baseline, the serum sCD26 level was abnormal in 11 (12%), and the sCD30 level was abnormal in 9 children (10%). Serum sCD26 correlated positively with age (<i>r</i> = 0.280, <i>P</i> = .008) and negatively with log-transformed serum sCD30 (<i>r</i> = -0.359, <i>P</i> = .001) and hs-CRP (<i>r</i> = -0.156, <i>P</i> = .04). In addition, log-transformed sCD30 correlated negatively with age (<i>r</i> = -0.304, <i>P</i> = .004) and height (<i>r</i> = -0.260, <i>P</i> = .01), and positively with a z score of respiratory resistance at 5 Hz (<i>r</i> = 0.230, <i>P</i> = .03). After adjustment by age, the association between sCD26 and hs-CRP was lost (<i>P</i> = .32), but the association between log-transformed

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Clinical Trial Registration: The original intervention study (Mäkelä MJ, Malmberg LP, Csonka P, Klemola T, Kajosaari M, Pelkonen AS. Salmeterol and fluticasone in children with multitrigger wheeze. Ann Allergy Asthma Immunol. 2012; 109:65–70.), on which this manuscript is based, was conducted at the time when international clinical trial registration sites were not commonly available (in 2002–2005), and the trial was registered in 2002 at the registry of Clinical Trials of Helsinki University Hospital.
Taking into account recent findings on hs-CRP and related cytokines in neonates with reduced lung function,9 it is plausible to surmise that similar uniform up-regulated cytokine profile may underlie pulmonary abnormalities seen in wheezy preschool children. Although FeNO levels decreased equally in the fluticasone and salmeterol-fluticasone groups during the intervention,1 the findings on peripheral blood inflammatory markers in the present study imply that the combination of inhaled glucocorticoid and long-acting β2-agonist (LABA) might have a synergistic anti-inflammatory effect. Such a synergistic effect has been proposed to be based on the increase in intracellular glucocorticoid receptor nuclear translocation.10 In contrast, in those receiving a LABA only, the increase in serum sCD26 concentration might be explained by resolution of inflammatory reactions by enhancing T\(_{H}1\) activity and/or by absence of a proapoptotic effect of glucocorticoids on inflammatory cells. Whether these findings are reproducible is an issue for further studies searching for optimal therapy response markers.

In conclusion, T\(_{H}2\) activation with the evidence of low-grade systemic inflammation may underlie pulmonary function abnormality in multiple-trigger wheezers. In addition, inhaled glucocorticoids combined with LABAs might have a synergistic effect on T\(_{H}2\)-mediated inflammatory responses.

### References

Linezolid desensitization in a pediatric patient

Linezolid is an antibacterial agent belonging to the oxazolidinone group that possesses bacteriostatic effects by inhibiting protein synthesis. Linezolid is effective against various gram-positive and gram-negative bacteria, including clinically important resistant microorganisms, such as methicillin-resistant Staphylococcus aureus and vancomycin-resistant Enterococcus. Hypersensitivity reactions rarely occur during linezolid treatment. In a study of 828 patients who were treated with linezolid, eruption and pruritus reactions rarely occurred during linezolid treatment. In a study of 828 patients who were treated with linezolid, eruption and pruritus were reported in only 1.7% of the patients. An 8-year-old girl with neuronal ceroid lipofuscinosis and progressive myoclonic epilepsy was taking multiple antibiotic treatments (preparation forms of the solutions are given in Table 1). The patient weighed 26 kg. Three different solutions containing the 0.02-, 0.2-, and 2-mg/mL concentrations of linezolid were prepared. However, the patient was premedicated with hydroxyzine and a corticosteroid, and the infusion rate was reduced to half. However, she again experienced generalized urticaria approximately 10 minutes after the initiation of infusion, and the infusion was interrupted. Although she was also taking other drugs, they were not given within 2 hours of the reaction. Because an antihistaminic drug was applied to our patient, linezolid hypersensitivity could not be confirmed. However, administration of linezolid treatment was necessary because of the clinical state of the patient. Moreover, the hypersensitivity reaction persisted despite administration of the antihistaminic drug and reduction in infusion speed; therefore, desensitization was chosen. There are 2 reported adult cases of linezolid desensitization. Cawley and Lipka treated a 41-year-old woman by oral desensitization using an intravenous form of the drug. Bagwell et al desensitized a 24-year-old woman using the intravenous form. In both cases, the patients were able to successfully take the drug without any reaction. In our case, the linezolid desensitization protocol applied by Bagwell et al was used with modifications (Table 1). The amount of the drug she would take was 10 mg/kg per dose every 8 hours, and the patient weighed 26 kg. Three different solutions containing 0.02-, 0.2-, and 2-mg/mL concentrations of linezolid were prepared (preparation forms of the solutions are given in Table 1). The desensitization protocol was completed in a total of 13 steps (2 doses from the first, 4 doses from the second, and 7 doses from the third) and within 4 hours 15 minutes (Table 1). After desensitization, the patient was able to take her linezolid treatment without reaction. In addition, the use of other drugs was continued after linezolid desensitization, and there were no reactions. We decided to perform skin tests under suitable conditions; however, they could not be performed because the patient stopped participation in the study owing to respiratory insufficiency.

To the best of our knowledge, this is the first case in the literature to describe a successful desensitization protocol with linezolid in a pediatric patient.

Hakan Guvenir, MD
Emine Dibek Misirioglu, MD
Muge Toyran, MD
Can N. Kocabas, MD

Department of Pediatric Allergy and Immunology
Ankara Children’s Hematology Oncology Training and Research Hospital
Ankara, Turkey

Division of Pediatric Allergy and Immunology
Department of Children’s Health and Diseases
Faculty of Medicine
Mugla Sikti Kocman University
Mugla, Turkey
cankocabas@yahoo.com

References


Disclosures: Authors have nothing to disclose.

Table 1

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<th>Rate, mL/h</th>
<th>Infusion duration, min</th>
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Abbreviation: min, minutes.

*Solution I is 2 mg of drug + 100 mL of 5% dextrose with water (D5W); concentration, 0.02 mg/mL. Solution II is 20 mg of drug + 100 mL of D5W (concentration, 0.2 mg/mL). Solution III is 600 mg of drug + 300 mL of D5W (concentration, 2 mg/mL).