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

Kotaniemi-Syrjänen, Anne

2016-08

http://hdl.handle.net/10138/224226
https://doi.org/10.1016/j.anai.2016.05.022

Downloaded from Helda, University of Helsinki institutional repository.
This is an electronic reprint of the original article.
This reprint may differ from the original in pagination and typographic detail.
Please cite the original version.
Serum soluble Th cell activity markers and high-sensitivity C-reactive protein in multiple-trigger wheezers

Deviation of immune responses toward Th2 cell reactions results in eosinophilic inflammation of the mucosa and increased responsiveness to various stimuli in the respiratory tract. Such Th2-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, Th1 cells other than Th2-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 Th1 cells, have been recognized. Serum soluble CD30 (sCD30), a marker of Th12-cell activation, has been associated with asthma and lung function and evaluated as a potential therapy response marker.

The role of serum soluble CD26 (sCD26), reflecting Th1 cell activity, seems to be more equivocal in the context of inflammation. Effects of anti-inflammatory treatment were less evident compared with Th2-type cytokines.

In our prior study, 105 children with multiple-trigger wheeze and evidence of bronchodilator responsiveness and/or exercise-induced bronchoconstriction were randomized to receiveinhaled 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. As a result of the intervention, exhaled nitric oxide fraction (FeNO) decreased and lung function (evaluated by impulse oscillometry) improved more in the fluticasone and salmeterol-fluticasone groups than in the salmeterol group. Moreover, lung function improved slightly more in the salmeterol-fluticasone group when compared with the fluticasone group. On this basis of this, we hypothesized that pulmonary function abnormalities observed in the cohort could be related to imbalance in activation of different Th cells 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. The intra-assay precisions were 8% and 6% and the interassay precisions were 15% and 14% for serum sCD26 and sCD30, respectively. Age- and sex-adjusted reference values were applied to define abnormal serum sCD26 and sCD30 levels. Interleukins 4, 10, and 13 were measured at baseline and after the intervention using the LINCOplex assay (Lincor Research Inc, St Charles, Missouri) and the Luminox R 100 TM instrument (Luminex Corp, Austin, Texas).

Serum high-sensitivity C-reactive protein (hs-CRP) was measured at baseline using the immunoturbidimetric assay (CRP; 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.

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.

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 τ statistic. To adjust for age in correlation analyses, analysis of covariance was performed. Differences between groups were analyzed by the χ² or Fisher exact test, τ test, Mann-Whitney U test, analysis of variance, or Kruskal-Wallis test. In repeated measurements, the τ test for paired samples or the Wilcoxon signed rank test was performed. To compare repeated measures 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 (r = 0.280, P = .008) and negatively with log-transformed serum sCD30 (r = −0.359, P = .001) and hs-CRP (r = −0.156, P = .04). In addition, log-transformed sCD30 correlated negatively with age (r = −0.304, P = .004) and height (r = −0.260, P = .01), and positively with a z score of respiratory resistance at 5 Hz (r = 0.230, P = .03). After adjustment by age, the association between sCD26 and hs-CRP was lost (P = .32), but the association between log-transformed

Disclosures: Authors have nothing to disclose.

Funding Sources: This study was funded by the Finnish Medical Foundation, Foundation for Pediatric Research, Foundation for Allergy Research, Sigrid Juslinus Foundation, and Helsinki University Central Hospital research funds.

Clinical Trial Registration: The original intervention study (Mäkelä MJ, Malmberg LP, Csonka P, Klemola T, Kajosaari M, Pelkonen AS. Salmeterol and fluticasone combination, 50/100 μg twice daily for 8 weeks. 1 As a result of the intervention, exhaled nitric oxide fraction (FeNO) decreased and lung function (evaluated by impulse oscillometry) improved more in the fluticasone and salmeterol-fluticasone groups than in the salmeterol group. Moreover, lung function improved slightly more in the salmeterol-fluticasone group when compared with the fluticasone group. On this basis of this, we hypothesized that pulmonary function abnormalities observed in the cohort could be related to imbalance in activation of different Th cells 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. The intra-assay precisions were 8% and 6% and the interassay precisions were 15% and 14% for serum sCD26 and sCD30, respectively. Age- and sex-adjusted reference values were applied to define abnormal serum sCD26 and sCD30 levels. Interleukins 4, 10, and 13 were measured at baseline and after the intervention using the LINCOplex assay (Lincor Research Inc, St Charles, Missouri) and the Luminox R 100 TM instrument (Luminex Corp, Austin, Texas). Serum high-sensitivity C-reactive protein (hs-CRP) was measured at baseline using the immunoturbidimetric assay (CRP; 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.

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.

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 τ statistic. To adjust for age in correlation analyses, analysis of covariance was performed. Differences between groups were analyzed by the χ² or Fisher exact test, τ test, Mann-Whitney U test, analysis of variance, or Kruskal-Wallis test. In repeated measurements, the τ test for paired samples or the Wilcoxon signed rank test was performed. To compare repeated measures 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 (r = 0.280, P = .008) and negatively with log-transformed serum sCD30 (r = −0.359, P = .001) and hs-CRP (r = −0.156, P = .04). In addition, log-transformed sCD30 correlated negatively with age (r = −0.304, P = .004) and height (r = −0.260, P = .01), and positively with a z score of respiratory resistance at 5 Hz (r = 0.230, P = .03). After adjustment by age, the association between sCD26 and hs-CRP was lost (P = .32), but the association between log-transformed
Markers.

issue for further studies searching for optimal therapy response in and/or by absence of a proapoptotic effect of glucocorticoids on clinical signifi-
cance. The results of the present study imply that the combination of inhaled glucocorticoid and salmeterol in those with elevated hs-CRP levels (n = 30) than in those without (n = 72) (geometric mean, 95.90 IU/mL; 95% CI, 90.20–102.00 IU/mL) (P = .03).

During the 8-week intervention, serum sCD26 increased significantly in the salmeterol group, and serum sCD30, interleukins 4, 10, and 13, and blood eosinophils decreased significantly in the salmeterol-fluticasone group but not in the fluticasone group (Table 1). The differences in repeated measurements be-
tween the intervention groups did not reach statistical significance (data not shown). The sample size was originally determined by targeting differences in FeNO 3 ; the results of the present study could have been strengthened if more stringent study participant selection was conducted based on sCD26 and sCD30 values of clinical significance.

Taking into account recent findings on hs-CRP and related cyto-
kines in neonates with reduced lung function, 1 it is plausible to surmise that similar uniform up-regulated inflammatory 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 β 2 -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 Th1 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, Th2 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 Th2-mediated inflammatory responses.

Anne Kotaniemi-Syrjänen, MD∗ Weronika Delezuch, MD L. Pekka Malmberg, MD Kari Punnonen, MD Irma H. Matinlauri, MD Anna S. Pelkonen, MD Mika J. Mäkelä, MD Skin and Allergy Hospital University of Helsinki and Helsinki University Hospital Helsinki, Finland ∗ISLAB Laboratory Centre Kuopio, Finland ∗HUSLAB Helsinki University Hospital Helsinki, Finland anne.kotaniemi-syrjanen@fi

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, 2.4% reported linezolid desensitization reactions, of which 0.3% with pruritus and urticaria were reported in only 1.7% of the patients.2

An 8-year-old girl with neuronal ceroid lipofuscinosis and progressive myoclonic epilepsy was taking multiple antibiotic treatments for septic arthritis and ventilator-associated pneumonia in the intensive care unit. On *Staphylococcus* growth in the blood culture, which was sensitive only to linezolid, the drug was added to the treatment. On day 7 of the treatment, she experienced urticaria on the face, neck, and body, without respiratory, digestive, or cardiovascular symptoms 20 minutes after starting linezolid infusion. The infusion was interrupted, and 1 mg/kg of hydroxyzine was administered. At the subsequent dose (after 8 hours), 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 Lipka3 treated a 41-year-old woman by oral desensitization using an intravenous form of the drug. Bagwell et al4 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.

**Table 1**

<table>
<thead>
<tr>
<th>Step</th>
<th>Solution*</th>
<th>Rate, mL/h</th>
<th>Infusion duration, min</th>
<th>Monitoring duration, min</th>
<th>Volume infused per mL</th>
<th>Dose administered with this step, mg</th>
<th>Cumulative dose, mg</th>
</tr>
</thead>
<tbody>
<tr>
<td>1 I</td>
<td>18</td>
<td>5</td>
<td>10</td>
<td>1.5</td>
<td>0.03</td>
<td>0.03</td>
<td></td>
</tr>
<tr>
<td>2 I</td>
<td>42</td>
<td>5</td>
<td>10</td>
<td>3.5</td>
<td>0.07</td>
<td>0.1</td>
<td></td>
</tr>
<tr>
<td>3 I</td>
<td>9</td>
<td>5</td>
<td>10</td>
<td>0.75</td>
<td>0.15</td>
<td>0.25</td>
<td></td>
</tr>
<tr>
<td>4 II</td>
<td>18</td>
<td>5</td>
<td>10</td>
<td>1.5</td>
<td>0.3</td>
<td>0.55</td>
<td></td>
</tr>
<tr>
<td>5 II</td>
<td>36</td>
<td>5</td>
<td>10</td>
<td>3</td>
<td>0.6</td>
<td>1.15</td>
<td></td>
</tr>
<tr>
<td>6 II</td>
<td>72</td>
<td>5</td>
<td>10</td>
<td>6</td>
<td>1.2</td>
<td>2.35</td>
<td></td>
</tr>
<tr>
<td>7 III</td>
<td>13.8</td>
<td>5</td>
<td>10</td>
<td>1.2</td>
<td>2.3</td>
<td>4.65</td>
<td></td>
</tr>
<tr>
<td>8 III</td>
<td>28.2</td>
<td>5</td>
<td>10</td>
<td>2.3</td>
<td>4.7</td>
<td>9.35</td>
<td></td>
</tr>
<tr>
<td>9 III</td>
<td>56.4</td>
<td>5</td>
<td>10</td>
<td>4.7</td>
<td>9.4</td>
<td>18.75</td>
<td></td>
</tr>
<tr>
<td>10 III</td>
<td>112.5</td>
<td>5</td>
<td>10</td>
<td>9.4</td>
<td>18.75</td>
<td>37.5</td>
<td></td>
</tr>
<tr>
<td>11 III</td>
<td>225</td>
<td>5</td>
<td>10</td>
<td>18.8</td>
<td>37.5</td>
<td>75</td>
<td>150</td>
</tr>
<tr>
<td>12 III</td>
<td>150</td>
<td>15</td>
<td>30</td>
<td>37.5</td>
<td>75</td>
<td>150</td>
<td>290</td>
</tr>
<tr>
<td>13 III</td>
<td>220</td>
<td>15</td>
<td>30</td>
<td>55</td>
<td>110</td>
<td>260</td>
<td></td>
</tr>
</tbody>
</table>

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). Stop when reaction is noted.

References


Disclosures: Authors have nothing to disclose.