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

Kotaniemi-Syrjänen, Anne

2016-08

Kotaniemi-Syrjänen , A , Delezuch , W , Malmberg , L P , Punnonen , K , Matinlauri , I H , Pelkonen , A S & Makela , M J 2016 , ' Serum soluble T-H cell activity markers and high-sensitivity C-reactive protein in multiple-trigger wheezers ' , Annals of Allergy, Asthma, & Immunology , vol. 117 , no. 2 , pp. 196-198 . https://doi.org/10.1016/j.anai.2016.05.022

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

publishedVersion

References

[1] Siddiqui AA, Berk SL. Diagnosis of *Strongyloides stercoralis* infection. *Clin Infect Dis*. 2001;33:1040–1047.
[2] Olsen A, van Lieshout L, Marti H, et al. *Strongyloidiasis*—the most neglected of the neglected tropical diseases? *Trans R Soc Trop Med Hyg*. 2009;103:967–972.
[3] Walzer PD, Milder JE, Banwell JG, Kilgore G, Klein M, Parker R. Epidemiologic features of *Strongyloides stercoralis* infection in an endemic area of the United States. *Am J Trop Med Hyg*. 1982;31:313–319.
[4] Grove DI. *Strongyloidiasis*: is it transmitted from husband to wife? *Br J Vener Dis*. 1982;58:271–272.
[5] Khieu V, Hattendorf J, Schar F, et al. *Strongyloides stercoralis* infection and re-infection in a cohort of children in Cambodia. *Parasitol Int*. 2014;63:708–712.
[6] Gyorkos TW, Genta RM, Viens P, MacLean JD. Seroepidemiology of *Strongyloides* infection in the Southeast Asian refugee population in Canada. *Am J Epidemiol*. 1990;132:257–264.
[7] Loutfy MR, Wilson M, Keystone JS, Kain KC. Serology and eosinophil count in the diagnosis and management of strongyloidiasis in a non-endemic area. *Am J Trop Med Hyg*. 2002;66:749–752.
[8] Genta RM, Weil GJ. Antibodies to *Strongyloides stercoralis* larval surface antigens in chronic strongyloidiasis. *Lab Invest*. 1982;47:87–90.
[9] Greiner K, Bettencourt J, Semolic C. Strongyloidiasis: a review and update by case example. *Clin Lab Sci*. 2008;21:82–88.
[10] Wehner JH, Kirsch CM, Kagawa FT, Jensen WA, Campagna AC, Wilson M. The prevalence and response to therapy of *Strongyloides stercoralis* in patients with asthma from endemic areas. *Chest*. 1994;106:762–766.

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

Deviation of immune responses toward T_H2 cell reactions results in eosinophilic inflammation of the mucosa and increased responsiveness to various stimuli in the respiratory tract. Such T_H2-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_H cells other than T_H2-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_H cells, have been recognized. Serum soluble CD30 (sCD30), a marker of T_H2-cell activation, has been associated with asthma and lung function[2] and evaluated as a potential therapy response marker.[2,3] The role of serum soluble CD26 (sCD26), reflecting T_H1 cell activity, seems to be more equivocal in the pathogenesis of asthma.[4,5] To date, there are no reports on the association of these T_H 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.[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.[1] Moreover, lung function improved slightly more in the salmeterol-fluticasone group when compared with the fluticasone group.[1] 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_H 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.[6] The intra-assay precisions were 8% and 6% and the interassay precisions were 15% and 14% for serum sCD26 and sCD30, respectively.[6] Age- and sex-adjusted reference values were applied to define abnormal serum sCD26 and sCD30 levels.[6] Interleukins 4, 10, and 13 were measured at baseline and after the intervention using the LINCOplex assay (Linco Research Inc, St Charles, Missouri) and the Luminex R 100 TM instrument (Luminex Corp, Austin, Texas).[7] 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.[8]

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.[8]

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 χ^2 or Fisher exact test, t test, Mann-Whitney U test, analysis of variance, or Kruskal-Wallis test. In repeated measurements, the t 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 ($r = 0.280$, $P = .008$) and negatively with log-transformed serum sCD30 ($r = -0.359$, $P = .001$) and hs-CRP ($\tau = -0.156$, $P = .04$). 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 Jusélius 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 in young children with multiple-trigger wheeze. *Ann Allergy Asthma Immunol*. 2012; 109:65–70[1]), 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.

Table 1
Change in the Levels of T_H1 and T_H2 Activation Markers, Associated Interleukins, and Blood Eosinophils With Regard to the 8-Week Intervention

Variable	Fluticasone propionate (n = 31)	Salmeterol-fluticasone (n = 30)	Salmeterol (n = 29)	*P* value
sCD26, mean (SD), ng/mL				
At baseline	1384.2 (320.2)	1487.7 (255.2)	1433.8 (220.5)	.33
After the intervention	1384.0 (242.5)	1455.4 (236.1)	1543.0 (266.2)	.051
P value for change	1.0	.38	.03	
sCD30, geometric mean (95% CI), IU/mL				
At baseline	97.5 (87.1–109.2)	97.2 (89.1–106.0)	100.0 (89.7–111.5)	.91
After the intervention	94.0 (79.1–111.6)	86.2 (76.6–96.9)	89.5 (79.6–100.7)	.66
P value for change	.67	.03	.12	
IL-4, median (IQR), pg/mL				
At baseline	1.6 (0.1–169.8)	20.2 (0.1–248.6)	48.9 (0.1–253.7)	.40
After the intervention	14.6 (0.1–141.3)	12.3 (0.1–212.2)	82.7 (0.1–211.3)	.54
P value for change	.39	.003	.34	
IL-10, median (IQR), pg/mL				
At baseline	12.5 (6.9–24.6)	12.7 (8.1–18.4)	10.9 (8.6–23.7)	.89
After the intervention	12.5 (8.0–20.7)	11.1 (5.5–18.7)	10.5 (7.3–34.2)	.36
P value for change	.81	.04	.14	
IL-13, median (IQR), pg/mL				
At baseline	21.1 (5.2–146.3)	20.8 (4.7–163.5)	60.5 (5.3–133.6)	.67
After the intervention	21.6 (6.2–128.6)	19.6 (3.6–124.2)	67.6 (4.8–122.3)	.66
P value for change	.25	.04	.34	
Blood eosinophil count, geometric mean (95% CI), $\times 10^9$/L				
At baseline	0.40 (0.30–0.52)	0.51 (0.39–0.68)	0.33 (0.23–0.45)	.08
After the intervention	0.35 (0.25–0.48)	0.41 (0.34–0.49)	0.39 (0.28–0.57)	.71
P value for change	.21	.03	.56	
Blood eosinophil percentage, median (IQR), %				
At baseline	6 (3–10)	7 (6–11)	7 (3–10)	.22
After the intervention	6 (3–10)	5 (4–8)	6 (4–11)	.73
P value for change	.28	.01	.76	

Abbreviations: CI, confidence interval; IL, interleukin; IQR, interquartile range; sCD26, soluble CD26; sCD30, soluble CD30.

sCD30 and height-adjusted respiratory resistance at 5 Hz *z* score remained statistically significant ($P = .02$). In addition, sCD30 was higher (geometric mean, 113.70 IU/mL; 95% CI, 96.60-133.80 IU/mL) in those with elevated hs-CRP levels (n = 15) 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 between the intervention groups did not reach statistical significance (data not shown). The sample size was originally determined by targeting differences in FeNO[1]; 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 cytokines in neonates with reduced lung function,[9] 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 T_H1 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_H2 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_H2-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@fimnet.fi

References

[1] Mäkelä MJ, Malmberg LP, Csonka P, Klemola T, Kajosaari M, Pelkonen AS. Salmeterol and fluticasone in young children with multiple-trigger wheeze. *Ann Allergy Asthma Immunol*. 2012;109:65–70.
[2] Purello-D'Ambrosio F, Gangemi S, Ruello G, Marotta G, Merendino RA. Effect of fluticasone propionate on soluble CD30 release in patients with severe allergic asthma. *J Investig Allergol Clin Immunol*. 2000;10:283–285.
[3] Kotaniemi-Syrjänen A, Delezuch W, Pelkonen AS, et al. Improvement in lung function is associated with a decrease in serum sCD30 in atopic infants. *Ann Allergy Asthma Immunol*. 2015;114:156–157.
[4] Lun SW, Wong CK, Ko FW, Hui DS, Lam CW. Increased expression of plasma and DC4+ T lymphocyte costimulatory molecule CD26 in adult patients with allergic asthma. *J Clin Immunol*. 2007;27:430–437.

[5] 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 Pædiatr*. 2011;100:e106–e111.
[6] 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.
[7] Hildesheim A, Ryan RL, Rinehart E, et al. Simultaneous measurement of several cytokines using small volumes of biospesimens. *Cancer Epidemiol Biomarkers Prev*. 2002;11:1477–1484.
[8] Schlenz H, Intemann T, Wolters M, et al. C-reactive protein reference percentiles among pre-adolescent children in Europe based on the IDEFICS study population. *Int J Obes*. 2014;38:S26–S31.
[9] Chawes BL, Stokholm J, Bønnelykke K, Brix S, Bisgaard H. Neonates with reduced neonatal lung function have systemic low-grade inflammation. *J Allergy Clin Immunol*. 2015;135:1450–1456.
[10] Usmani OS, Ito K, Maneechotesuwan K, et al. Glucocorticoid receptor nuclear translocation in airway cells after inhaled combination therapy. *Am J Respir Crit Care Med*. 2005;172:704–712.

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*.[1] Hypersensitivity reactions rarely occur 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.[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 Lipka[3] treated a 41-year-old woman by oral desensitization using an intravenous form of the drug. Bagwell et al[4] 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.

Table 1
Linezolid Intravenous Desensitization Protocol

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

Abbreviation: min, minutes.
[a]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).

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 Misirlioglu, 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 Sitki Kocman University
Mugla, Turkey
cankocabas@yahoo.com

References

[1] Ager S, Gould K. Clinical update on linezolid in the treatment of gram positive bacterial infections. *Infect Drug Resist*. 2012;5:87–102.
[2] Birmingham MC, Rayner CR, Meagher AK. Linezolid for the treatment of multidrug-resistant, gram-positive infections: experience from a compassionate-use program. *Clin Infect Dis*. 2003;36:159–168.
[3] Cawley M, Lipka O. Intravenous linezolid administered orally: a novel desensitization strategy. *Pharmacotherapy*. 2006;26:563–568.
[4] Bagwell AD, Stollings JL, White KD, Fadugba OO, Choi JJ. Linezolid desensitization for a patient with multiple medication hypersensitivity reactions. *Ann Pharmacother*. 2013;47:e30.

Disclosures: Authors have nothing to disclose.