



ORIGINAL ARTICLE / ОРИГИНАЛНИ РАД

Comparison between serum levels of interleukin-33 in children with allergic asthma before and after inhalatory corticosteroid treatment

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Introduction/Objective Interleukin 33 (IL-33) has a very significant function in inflammatory and autoimmune mechanisms, but its significance in immunopathogenic mechanisms of different allergic diseases, including allergic asthma (AA), is becoming increasingly emphasized.

The objective of the study was to investigate serum levels of IL-33 in children with AA before applying inhalation corticosteroid therapy (ICS Th) and six months after it, correlating the gathered values of IL-33 with some clinical traits of the patient.

Methods The serum value of IL-33 has been determined in 61 children with AA before starting treatment and six months after treatment with ICS Th, and this was repeated in 30 healthy children.

Results Values of IL-33 in serum are significantly higher in children with AA that have not been treated with ICS Th during six months ($p = 0.00$; $p < 0.05$), which is also the case when comparing with healthy children ($p = 0.00$; $p < 0.05$). Serum values of IL-33 in children with AA after six months of ICS Th and in healthy children do not show significant difference ($p = 0.88$; $p > 0.05$). The correlation between serum values of IL-33 before applying ICS Th and the severity, degree of AA control, and the applied dose of ICS Th is statistically significant and positive.

Conclusion IL-33 values in the serum are significantly higher in children with untreated AA in those with poorly controlled AA. Six-month treatment with ICS Th leads to significant reduction of IL-33 serum levels, whose values are in positive correlation with the severity and control of AA.

Keywords: interleukin-33; asthma; anti-inflammatory medication

INTRODUCTION

Allergic asthma (AA) is a leading chronic disease in children, its incidence in the last decades is on the constant increase globally, as well as in Serbia. The newest prevalence estimates across the world indicate that 334 million people suffer from AA. It is estimated that the number of people with asthma will increase to over 400 million until 2025 [1].

Asthma is a chronic inflammatory disease of the airways that is characterized by episodes of reversible airway obstruction, bronchial hyperactivity, and chronic lung inflammation [2].

Interleukin-33 (IL-33) was initially identified in small veins with high endothelia when it was determined that it has similar molecular properties with certain members of IL-1 superfamily (IL-1 α , IL-1 β , IL-1Ra and IL-18) [3, 4, 5].

IL-33 can have pro- and anti-inflammatory and protective roles, so IL-33 represents a subject of numerous researches in order to clarify the precise role of this cytokine in inflammatory diseases [6–9].

Many studies had as its aim the investigation of the exact role of IL-33 and ST2 receptors in Th2 mediated disorders. In most cases results pointed out that IL-33/ST2 axes stimulates the Th2 inflammatory response [10, 11, 12].

In the AA etiopathogenesis, inflammatory cells and mediators that belong to the Th2 immune response, eosinophil and basophil granulocytes and mast cells have the key role. Environmental antigens like infections (virus, bacterial), allergens, and air pollution induce Th2 immune response that results with a release of appropriate cytokines by epithelial cells. The function and significance of individual cytokines, among them IL-33, in patients suffering from AA, especially in children, are not precisely known [13, 14].

Up until now, research emphasizes the importance of IL-33 in initiating the differentiation of naïve CD4+ T cells and their maturation into Th2 cells that through their own specific cytokine profile lead to the activation of eosinophil granulocytes that support allergic inflammation, or create predispositions in an individual for the development of asthma and its exacerbation [15]. The direct influence of mast cells leads to the releasing of TNF that specifically emphasizes antigen sensitization. Indirectly through mast cells and IL-13, IL-33 induces eosinophilia and hyper-reactivity of airways [16, 17].

IL-33 is dominantly a product of tissue cells, although active leukocytes that are a classical source of other para-inflammatory cytokines present a significant source of this cytokine [5].

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Tissue damage that occurs as a consequence of infection of exposure to hypersensitive individuals to an allergen can lead to the release of IL-33 [15, 18].

Results of other studies conducted on those suffering from AA have shown an absence of correlation between serum IL-33 levels and other parameters of allergic inflammation (for instance eosinophils in blood, cumulative IgE in blood) in persons with low atopic status, while in those with high atopic status this correlation is present [19]. The explanation lies in the fact that IL-33 shows primarily the characteristics of a proinflammatory marker, while serum IgE and eosinophil granulocytes represent significant markers in the estimation of atopic status, but not the degree of inflammation [20, 21].

METHODS

We have performed a prospective study at the Institute for Child and Youth Health Care of Vojvodina in the period between September 2016 and March 2018. The study encompassed 61 children aged 6–18 years with the diagnosis of AA. The control group comprised 30 healthy children of the same sex and age as the children in the studied group.

Study protocol has been approved by the Ethical Commission (Faculty of Medicine in Novi Sad, Institute for Child and Youth Health Care of Vojvodina, Clinical Center of Vojvodina). Signed informed consent has been obtained from all the parents, and from children older than 10 years. The study has been performed adhering to the principles of the Helsinki Declaration.

Inclusion criteria in the study group were age of 6–18 years with a newly established diagnosis of light to mild AA, or subjects with light to mild AA diagnosed earlier but without ICS prophylaxis at least six months before inclusion into the study. Diagnosis and classification have been performed by Global Initiative for Asthma (GINA) guidelines [2].

Exclusion criteria were the following: existence of atopic dermatitis, urticaria, food allergies, chronic respiratory infections, uncontrolled gastro-esophageal reflux, eosinophilic esophagitis, parasitic infection, any other chronic infection, allergen-specific immunotherapy (in the period prior to and during the study), acute infections and other acute illnesses, use of systemic corticosteroids immediately before and during the planned study.

Children that comprised the study group underwent two additional examinations after the initial one, three and six months after the treatment. Anamnestic and hetero-anamnestic data for the first and the second control period were taken from all children in the study group. The type of difficulty, the need for using short-acting beta-2 agonist, and the frequency of its use were especially noted. We performed a clinical examination and specially noted the following: body mass and weight, nutrition levels (BMI, Z score, and percentiles), vital parameter values and transcutaneous oxygen saturation of hemoglobin as well as findings of a physical lung examination. All the examines underwent an investigation of lung functioning using the MasterScreenIOS spirometer (Jaeger, Germany) according to American Thoracic Society guidelines.

During the first examination and the follow-up six months later, all the participants underwent laboratory examinations that, amongst other things, encompassed determining levels of IL-33 in the serum. The measurement of IL-33 levels was performed at the laboratory of the Clinical Center of Vojvodina in Novi Sad. The levels were determined via direct sandwich enzyme-linked immunosorbent assay test that contains recombinant human IL-33 and polyclonal antibodies specific for IL-33 (Human IL-33 Quantikine® ELISA, Research and Diagnostic Systems, Inc., Minneapolis, MN, USA). According to the specifications of the manufacturer, the minimal detectable level of IL-33 that can be determined by using this test is 0 pg/ml. All procedures have been performed by following the instructions of the manufacturer. The intensity of the colored reaction was determined by an automatized immunochemical analyzing device ChemWell (Awareness Technology, Inc., Palm City, FL, USA). Absorbance was measured at 450 nm filter via standard curve of serially diluted standards. By using the standard curve, we determined the levels of IL-33 in all 91 participants.

The therapeutic approach in asthma treatment to all the participants was in accordance to GINA recommendations for the treatment of mild and medium asthma, i.e. appropriately dosed ICS therapy was applied in all cases. During the study, on the follow-up examinations at three and six months from the beginning of ICS therapy, AA difficulty based on GINA recommendations was determined based on the level of control (controlled, partially controlled, uncontrolled) and treatment intensity (low, medium, high ICS dosages).

All the children in the control group underwent the following: anamnesis/hetero-anamnesis taken (except the information whether the child is being investigated for oversensitivity to any medication, the information pertaining to the exclusion from the study was especially noted, like the absence of difficulties and signs of acute infections two weeks before the examination, absence of chronic diseases). We performed a clinical examination and the following were especially noted: mass, height, nutrition level (BMI, Z score, and percentile), absence of clinical signs of infection. The level of IL-33 (pg/ml) in the serum was determined in the same way as in the investigated group.

Statistical analysis

Wilcoxon pair test, t-test for independent samples, Mann-Whitney U-test, median test, and χ^2 test were used for the determination of statistical significance. Spearman's rank correlation coefficient was used to determine correlation. The value of $p < 0.05$ was considered statistically significant. Data processing was performed by the statistical program package IBM SPSS Statistics, Version 23.0 (IBM Corp., Armonk, NY, USA).

RESULTS

Out of the total number of participants ($n = 61$) with an average age of nine years and six months, 32 (52.5%)

were boys and 29 (47.5%) were girls. The control group (n = 30) was made up of healthy children with an average age of nine years and eight months, 16 (53.3%) boys and 14 (46.6%) girls (Table 1).

The severity and degree of AA control that the participants experienced after three and six months of ICS Th as well as the ICS dose that the participants received during the first three months and between the third and sixth month of ICS Th are displayed in Table 1.

IL-33 level values (pg/ml) in the investigated group before the application of ICS Th and six months after ICS Th are presented in Table 2, in which values of serum IL-33 (pg/ml) in the control group are presented as well.

Participant grouping with regards to serum IL-33 levels that the participants had before and after ICS Th are presented in Table 3.

Children that suffered from AA before commencing ICS therapy had significantly higher values of IL-33 than healthy children of the same age ($U = 509$; $p = 0.00$; $p < 0.01$).

In children where AA treatment has not commenced, IL-33 serum values were significantly higher compared to those that underwent six months of ICS Th ($Z = -4.394$; $p = 0.00$; $p < 0.01$). It has been determined that children suffering from AA that have elevated values of IL-33 in the serum before ICS treatment also register higher IL-33 levels after six months of ICS therapy ($r_s = 0.271$; $p = 0.04$; $p < 0.05$).

Results show that children with AA that have undergone six months of ICS Th do not show statistical differences in serum IL-33 levels of healthy children of the same age ($U = 897$; $p = 0.88$; $p > 0.05$) (Table 4).

In Table 4 we present serum values of IL-33 (before and after six months of ICS Th) referenced by AA severity and control level (the children had three and six months from the introduction of ICS therapy) and applied medication dosages (during the first and second trimester of ICS Th).

DISCUSSION

In our study, we analyzed the levels of IL-33 in the serum of children 6–18 years old with AA and in healthy children. The average levels of IL-33 were higher in children with AA before ICS therapy (2.550 ± 3.387 pg/ml). Lower values of IL-33 in the serum were detected in children after six months of ICS therapy, with an average value of 0.838 ± 1.394 pg/ml. The lowest level of serum IL-33 was measured in healthy children and it amounted to 0.573 ± 0.632 pg/ml.

It has been determined that IL-33 serum levels are significantly higher in children that suffer from AA before the beginning of treatment concerning healthy children. Similar findings have been found in the research by Bahrami et al. [22], according to which IL-33 levels in 61 children with asthma were compared with IL-33 levels of children in the control group, those without asthma, and the results were statistically significant. In the study, average values of IL-33 in the serum of children with asthma was 15.17 ± 32.3 pg/ml. Higher IL-33 serum levels in children that suffer from

Table 1. Division of participants by asthma severity and control levels in the third and sixth month of inhalation corticosteroid therapy (ICS Th), as well as ICS dosages administered during the first three months and in the period from third to sixth month

Asthma severity and control levels	After 3 months of ICS Th		After 6 months of ICS Th	
	Number of participants	Percentage	Number of participants	Percentage
Asthma severity				
Light	46	75.4%	39	63.9%
Medium difficulties	15	24.6%	18	29.5%
Difficult	0	0%	4	6.6%
Asthma control				
Controlled	59	96.7%	45	73.8%
Partially controlled	2	3.3%	15	24.6%
Uncontrolled	0	0%	1	1.6%
ICS medication dose	During first 3 months	From third to sixth month		
Low	23	37.7%	47	77%
Medium	38	62.3%	14	23%

Table 2. Values of IL-33 serum levels (pg/ml) in the investigated group (before and six months after inhalation corticosteroid therapy (ICS Th) and in the control group

Investigated group	n	Min.	Max.	Mod	M	Mean	SD
Before ICS Th application	61	0.00	14.74	0.04	1.49	2.55	3.39
After 6 months of ICS Th application	61	0.00	7.8	0	0.26	0.83	1.39
Control group	30	0.00	2.68	0	0.26	0.57	0.63

Mod – most common value; M – medial value; SD – standard deviation; IL-33 – interleukin 33

Table 3. Participants grouped by interleukin 33 (IL-33) serum levels before and after six months of inhalation corticosteroid therapy (ICS-Th)

Participant groups based on IL-33 levels	n	%
Higher values before ICS Th	45	73.8
Higher values after ICS Th	13	21.3
Same values before and after ICS Th	3	4.9
Total	61	100

Table 4. Relationship between interleukin 33 (IL-33) values in the serum with allergic asthma (AA) severity and control level, and ICS dose

Clinical indicators of the inflammation level	Before ICS Th-IL-33 (pg/ml)		After six months of ICS Th-IL-33 (pg/ml)	
	r_s	p	r_s	p
AA severity – 3 months ICS Th	0.52**	0.00	0.23	0.08
AA severity – 6 months ICS Th	0.42**	0.00	0.45**	0.00
AA control – 3 months ICS Th	0.29*	0.02	0.14	0.28
AA control – 6 months ICS Th	0.39**	0.00	0.39**	0.00
Medication dose: first 3 months of ICS Th	0.08	0.56	-0.02	0.87
Medication dose: second 3 months of ICS Th	0.48**	0.00	0.16	0.20

ICS Th – inhalation corticosteroid therapy;

r_s – Spearman rank correlation coefficient;

* $p < 0.05$;

** $p < 0.01$

asthma detected in the study by Bahrami et al. [22] than in those detected in our study can be explained by differences in inclusion criteria. In the research by Bahrami et al. [22], participants with AA were included regardless of the length (intermittent, persistent) and asthma severity (light, intermediary, severe) in contrast to our study, where participants with only the characteristics of persistent, light, and intermediary asthma were included. Other studies that compared IL-33 levels in children with AA with those in healthy children also produced similar results. A meta-analysis that encompassed eight previously conducted studies that cumulatively had 330 children with asthma and 248 healthy children shows that IL-33 serum levels were higher in children with asthma than in healthy children [23].

IL-33 serum values in healthy children that are in the control group of participants in our study are similar to those reported by other studies of pediatric populations. For instance, the average value of IL-33 in the serum of healthy children in the Iranian population was 0.61 ± 2.16 pg/ml [24]. But the results of research done on healthy adult population show higher IL-33 values that those detected in healthy children in our study. This fact suggests that patient age can be a significant factor in defining the normal span of IL-33 serum levels, and this is significant for interpreting laboratory findings in regular everyday practice.

Our study shows that after six months of ICS therapy in children that suffer from AA, there is a significant decrease in serum IL-33 levels. We did not find similar research in the literature available to us.

The influence of ICS on IL-33 in AA and their correlation is unclear. Studies performed on cell cultures have pointed out the significance of IL-33 for the creation of corticosteroid resistance. Namely, the research conducted by Kabata et al. [25] suggest that one of the potential mechanisms leading to corticosteroid resistance that can emerge in Th2-mediated inflammation of the air ways does so because of the influence of IL-33 on natural helper cells. These represent a sort of lymphoid cells of type 2 inborn immunity, i.e. resistance can emerge as a consequence of IL-33-mediated proliferation and production of type 2 cytokines from said cells. In vitro research on cell cultures shows that corticosteroids have a relatively efficient anti-inflammatory effect on IL-33-mediated inflammation [26].

In our study, children with AA that underwent six months of ICS treatment do not differ in IL-33 serum levels from healthy children of the same age. Studies that compared IL-33 serum levels before and after ICS therapy have not been found in the available literature. Similar values of IL-33 in the serum in children with AA after six months of ICS and in healthy children and the significant fall of IL-33 six months after ICS therapy can firstly be explained by the aforementioned anti-inflammatory effects of ICS. In addition, the results of our research can be explained by the characteristics of the participant group itself. Children included in our study had exclusively light and medium asthma severity, while patients with severe forms of asthma and patients that required additional treatment in order to control their illness (long-acting beta-agonist, combination of ICS and long-acting beta-agonist, systemic corticosteroids) were

excluded from our study. Maintaining high values of IL-33 despite the application of ICS monotherapy can perhaps be expected in patients with the severe and/or steroid resistant form of AA, which is not the subject of our study.

The incidence of participants regarding the severity and the degree of AA control in our research is a direct consequence of inclusion and exclusion criteria of our study.

In our research the patients that had higher levels of IL-33 before ICS prophylaxis had a more severe form of AA during the follow up period, and worse control of asthma during the treatment period and they required higher dosages of ICS in the second trimester of treatment. Patients that after six months of ICS prophylaxis still had a severe form and worse control of AA had higher IL-33 levels in the serum. The connection of IL-33 and severity of AA is documented in other studies. Research performed by Bahrami et al. [22] on children with asthma has also shown a correlation between IL-33 in the serum and asthma severity. The lowest IL-33 serum levels were detected in children with mild asthma, somewhat higher values in children with medium severity asthma, and the highest ones in those with severe asthma [22]. In addition, studies conducted on adult populations have shown a significant difference in IL-33 values between patients with intermittent, light, medium severe, and severe persistent asthma [27]. Guo et al. [28] in a study conducted on 45 adult participants have shown a positive correlation between IL-33 levels in the serum and the thickening of the basal membrane in bronchial biopsy samples and asthma severity. Lower values of IL-33 after six months of ICS monotherapy application confirm the anti-inflammatory effect of ICS and its suppressive potential on pro-inflammatory cytokines. Lower degrees of control and severe form of AA in participants that had higher values of IL-33 before and after six months of ICS therapy show that IL-33 can be a useful marker when choosing the therapy type and dosage, i.e. contributing to the optimal treatment of AA.

CONCLUSION

Results of our research and the cited results of other studies suggest that serum IL-33 can represent a potent biomarker for the severity of AA. The great importance of determining IL-33 serum levels during diagnostic evaluation of AA before starting the treatment shows a potential for better defining the asthma phenotype and with it an earlier optimization of therapy.

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Conflict of interest: None declared.

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Поређење серумских нивоа интерлеукина-33 код деце са алергијском астмом пре и после шестомесечне инхалаторне кортикостероидне терапије

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САЖЕТАК

Увод/Циљ Интерлеукин-33 (ИЛ-33) има веома битну функцију у инфламаторним и аутоимунским механизмима, али се све више истиче и значај у имунопатогенетским механизмима различитих алергијских обољења, укључујући и алергијску астму (АА). Циљ овог рада је испитивање серумских вредности ИЛ-33 код деце са АА пре и после шест месеци примене инхалаторне кортикостероидне терапије (*ICS Th*) и корелације добијених вредности ИЛ-33 са појединим клиничким особинама ових болесника.

Методe Одређена је серумска вредност ИЛ-33 код 61 детета са АА пре започињања лечења и шест месеци после третмана са *ICS Th*, као и код 30 здраве деце.

Резултати Вредности ИЛ-33 у серуму су значајно веће код деце са АА која нису лечена у односу на децу са АА код којих

је спровођена *ICS Th* током шест месеци ($p = 0,00$; $p < 0,05$), као и у односу на здраву децу ($p = 0,00$; $p < 0,05$). Серумске вредности ИЛ-33 код деце са АА после шест месеци *ICS Th* и код здраве деце не показују значајне разлике ($p = 0,88$; $p > 0,05$). Корелација између серумских вредности ИЛ-33 пре примене *ICS Th* и тежине, степена контроле АА као и примењене дозе *ICS Th* је статистички значајна и позитивна.

Закључак Вредности ИЛ-33 у серуму су значајно веће код деце са АА која нису лечена и код којих је АА лоше контролисана. Третман са *ICS Th* током шест месеци доводи до значајне редукције серумских нивоа ИЛ-33, чије вредности су у позитивној корелацији са тежином и контролом АА.

Кључне речи: интерлеукин-33; астма; дете; антиинфламаторни лекови