University of Novi Sad, Faculty of Medicine Novi Sad
Institute of Child and Youth Health Care of Vojvodina, Pediatric Clinic, Novi Sad
Clinical Center of Vojvodina, Novi Sad, Center for Laboratory Medicine

Original study
Originalni naučni rad
UDK 616.248:577.112.85]-053.2
https://doi.org/10.2298/MPNS2004088SM

COMPARISON OF SERUM INTERLEUKIN-33 LEVELS IN CHILDREN WITH ALLERGIC RESPIRATORY DISEASES

Borko MILANOVIĆ, Gordana VIJATOV DURIĆ, Mirjana STOJŠIĆ, Aleksandra MILUTINOVIC and Jelena STOJČEVIĆ MALETIĆ

Summary
Introduction. Recent studies point to the importance of interleukin-33 in the pathogenesis of allergic respiratory diseases. The relationship of interleukin-33 and certain allergic respiratory diseases as well as their characteristics is not fully elucidated. The basic aim of this research was to determine interleukin-33 serum levels in children with allergic asthma and allergic rhinitis, as well as to examine the relationship between obtained interleukin-33 levels and individual clinical characteristics of these patients. Material and Methods. Serum interleukin-33 levels were measured in a total of 91 children. The study group included 39 children with both allergic asthma and allergic rhinitis, and also 22 children with allergic asthma without allergic rhinitis. The control group included 30 healthy children. Results. Serum levels of interleukin-33 in children with both allergic asthma and allergic rhinitis were significantly higher compared to those in children with allergic asthma only (χ² = 7.01; p = 0.008; p < 0.01). Both groups of patients had significantly higher interleukin-33 serum levels compared to healthy children (χ² = 7.01; p = 0.008; p < 0.01). The correlation between serum interleukin-33 levels and allergic asthma severity was statistically significant (rs = 0.289; p < 0.05). Conclusion. Serum levels of interleukin-33 were significantly higher in children with allergic respiratory diseases compared to healthy examinees. Significantly higher levels of serum interleukin-33 levels were found in children with both allergic asthma and allergic rhinitis, compared to children with allergic asthma only. Patients with higher interleukin-33 serum levels also had a more severe type of allergic asthma.

Key words: Interleukin-33; Respiratory Tract Diseases; Interleukins; Allergens; Respiratory Hypersensitivity; Child; Rhinitis, Allergic; Asthma; Hypersensitivity, Immediate

Sažetak
Uvod. Dosadašnja ispitivanja ističu izraznu važnost interleukina-33 u patogeniji alergijskih bolesti disajnih puteva. Odnos interleukina-33 i pojedinih alergijskih bolesti disajnih puteva kao i njihovih karakteristika nije dovoljno preciziran. Osnovni cilj ovog istraživanja bio je odrediti vrednosti interleukina-33 u serumu kod dece sa alergijskom astmom i alergijskim rinitem kao i ispitati odnos dobijenih vrednosti interleukina-33 sa pojedinim kliničkim karakteristikama ovih pacijenata. Mjerilo i metode. Izmerene su serumске vrednosti interleukina-33 kod ukupno 91 deteta. Ispitivanu grupu činilo je 39 dece sa alergijskom astmom i alergijskim rinitem i 22 deteta koja su imala alergijsku astmu bez alergijskog rinitema. Kontrolnu grupu činilo je 30 zdrave dece. Rezultati. Obe grupe pacijenata su imale statistički značajne veće vrednosti interleukina-33 u serumu u odnosu na decu koja su imala alergijsku astmu bez alergijskog rinitema (χ² = 7.01; p = 0.008; p < 0.01). Obe grupe pacijenata su imale statistički značajne veće vrednosti interleukina-33 u serumu u odnosu na zdrave dete (χ² = 7.01; p = 0.008; p < 0.01). Korelaciju između vrednosti interleukina-33 u serumu i težine alergijske astme je statistički značajnu (rs = 0.289; p < 0.05). Zaključak. Serumsko bolestima disajnih puteva u odnosu na zdrave ispitanike, značajno više vrednosti interleukina-33 u serumu imaju dece sa alergijskom astmom i alergijskim rinitemom u odnosu na decu sa alergijskom astmom bez alergijskog rinitema. Pacijenti koji su imali više vrednost interleukina-33 u serumu imali su i teži oblik alergijske astme.

Ključne reči: interleukin-33; oboljenja respiratornog sistema; interleukini; alergeni; respiratorna hiperosetljivost; dete; alergijski rinitis; astma; atopijska hiperosetljivost
consequence of type 2 T helper cells (Th2) activation, while mechanisms of “non-Th2” mediated inflammation are still poorly defined [3].

Interleukin-33 (IL-33) is a relatively new member of cytokine interleukin 1 family. Research studies published so far showed that IL-33 appears to have proinflammatory, anti-inflammatory and protective function in different diseases. Determination of IL-33 function in certain inflammatory diseases has been the subject of numerous ongoing researches [4–7]. The IL-33 has a significant role in the differentiation of naïve cluster of differentiation 4 (CD4+) T cells into Th2 cells which cause activation of eosinophils and other inflammatory cells by complex cytokine- and cell-mediated interaction, thereby significantly impacting allergic inflammation in AA and allergic rhinitis (AR) [8]. Previous studies showed that there was a higher level of serum IL-33 in patients with AA compared to healthy examinees [9–11]. The relationship between serum IL-33 level and certain clinical characteristics of allergic respiratory diseases is not specified enough, especially in children. The basic aim of this research was to determine serum IL-33 levels in children with AA and AR, as well as to examine the relationship between obtained IL-33 levels and individual clinical characteristics of these patients.

Material and Methods

A prospective study was conducted at the Institute of Child and Youth Health Care of Vojvodina from September 2016 to March 2018. The study was approved by Ethics Committee of the Faculty of Medicine in Novi Sad and Institute of Child and Youth Health Care of Vojvodina. Informed consent and assent (for children aged 10 years and older) were obtained prior to inclusion into the study. The principles of the Declaration of Helsinki were respected during the trial.

The study group included 61 children, aged between 6 and 18 years, with mild or moderate clinical presentation of AA (newly and previously diagnosed children who did not receive prophylaxis with inhaled corticosteroids at least 6 months before the trial). The diagnostic protocol and classification of AA severity were performed according to Global Initiative for Asthma (GINA) guidelines [1].

Thirty healthy examinees were included in the control group and they were matched on sex and age with the study group.

The exclusion criteria were as follows: presence of urticaria, eczema, food allergies, chronic respiratory infections, parasite infections, uncontrolled gastroesophageal reflux, eosinophilic oesophagitis, any chronic disease, acute infection or other acute condition, earlier or current treatment with allergen specific immunotherapy and use of systemic, inhalatory, intranasal and local corticosteroids before and during the study.

Anamnestic/heteroanamnestic data were obtained for children of the study group. The type of symptoms and frequency of short-acting beta2-agonists (SABA) administration were recorded. The clinical examination was performed and the following parameters were recorded: weight and height, body mass index (BMI), Z score, percentiles. Pulmonary function test – spirometry was performed in all children of the study group by using MasterScreen IOS (Jaeger, Germany) spirometer, according to American Thoracic Society (ATS) instructions.

According to Allergic Rhinitis and its Impact on Asthma (ARIA) recommendations, classification of AR was made based on the medical history data and clinical laboratory test results in the study group, to establish children who had been diagnosed with both AA and AR [12]. Based on the severity, AR cases were classified as mild and moderate/severe; in regard to the causal allergic type as perennial and seasonal, and based on the duration of symptoms as intermittent and persistent.

Laboratory tests also included determination of serum IL-33 levels in all the children in both the study and control group. Measurement of serum IL-33 levels was performed in the laboratory of the Clinical Center of Vojvodina, Novi Sad. The IL-33 levels were determined by direct (sandwich) enzyme linked immunosorbent assay (ELISA), a method which implies the use of Human IL-33 Quantikine®ELISA assay (R&D systems, USA) and polyclonal antibodies specific for IL-33 that was carried out on EUROIMMUN Analyzer I 2–P ELISA (EUROIMMUN AG, Luebeck, Germany) according to the manufacturer’s protocol.

Anamnestic/heteroanamnestic data were collected for children in the control group (drug hypersensitivity, absence of acute infection signs and symptoms 2 weeks before examination, while absence of chronic diseases was specially recorded). Physical examination was also performed (weight, height and absence of clinical signs of acute infection were specially recorded). Serum IL-33 level (pg/ml) was measured in the same way in both groups of children.

The Statistical Package for the Social Sciences 23 was used for the statistical processing of the obtained data. Estimation of statistical significance was done by using Wilcoxon signed-rank test, independent samples T-test, Mann-Whitney U-test, median test and chi-squared test. Spearman’s rank correlation coefficient was used for correlation assessment and p < 0.05 was considered statistically significant.
Results

The study group included 61 children (n = 61), average age of 9 years and 6 months. Thirty-two (52.5%) examinees were boys and 29 (47.5%) were girls. The control group included 30 healthy children (n = 30), average age of 9 years and 8 months; 16 (53.3%) of them were boys and 14 (46.6%) girls. In the study group 52 (85.2%) patients had normal weight, 4 (6.6%) were overweight, 3 (4.9%) were obese and 2 (3.3%) were underweight. The control group included 25 (83.3%) examinees with normal weight, 4 were (13.3%) overweight and 1 was (3.3%) obese, while there were no underweight examinees.

Differences in sex ($\chi^2 = 0.006; p = 0.937$), age ($t = 0.187; p = 0.852$) and obesity level ($\chi^2 = 2.157; p = 0.540$) between the study and control group were not statistically significant ($p > 0.05$).

Table 1 shows serum IL-33 levels in children from the study group, i.e. in children with AA and with/without AR and also in healthy children in the control group.

Mann-Whitney U-test results show that there is a highly statistically significant difference ($U = 509; p = 0.00; p < 0.01$) in the serum IL-33 levels between the children aged 6 – 18 years with AA/without AR and healthy children of the same age.

Out of the total of 61 children with AA who participated in this study, 39 (64%) also had AR. The remaining 22 (36%) children had AA without AR.

The median serum IL-33 level in children with AA and AR was 1.80 pg/ml, which is above the median serum IL-33 level in the whole sample (1.49 pg/ml). The median serum IL-33 level in children without AA was 0.70 pg/ml, i.e. they had lower median levels compared to the median level in the whole sample ($M = 1.49$ pg/ml). The examinees who had extremely high serum IL-33 levels in regard to the median levels of other examinees in the group are shown in Graph 1.

The chi-square test showed that children with both AA and AR also had statistically significantly higher serum IL-33 levels compared to the children with AA but without AR ($\chi^2 = 7.01; p = 0.008; p < 0.01$).

The majority of examinees (34 children, 55.7%) presented with a mild AA, while 27 (44.3%) presented with moderate AA symptoms.

The relationship between serum IL-33 levels and AA severity was analyzed by Spearman’s rank correlation coefficient. A statistically significant positive correlation was found between serum IL-33 level and AA severity ($rs = 0.289; p = 0.024; p < 0.05$).

Table 2 shows the prevalence of perennial and seasonal, mild and moderate/severe, intermittent and persistent AR relative to the median level of serum IL-33 in the whole sample.

The chi-square test results did not indicate that there was a statistically significant difference among serum IL-33 levels in the examinees with perennial and seasonal AR ($\chi^2(1) = 0.14; p = 0.707; p > 0.05$).

### Table 1. Serum interleukin-33 levels (pg/ml) in the study and control group

|                      | Study group/Ispitivana grupa | Control group/Kontrolna grupa |
|----------------------|-----------------------------|-------------------------------|
| N                    | 61                          | 30                            |
| Min.                 | 0.00                        | 0.00                          |
| Max.                 | 14.745                      | 2.682                         |
| Mode                 | 0.041                       | 0.00                          |
| M                   | 1.491                       | 0.261                         |
| AM                  | 2.550                       | 0.573                         |
| SD                  | 3.387                       | 0.632                         |

Legend: N - number of examinees; Min. - minimal; Max. - maximal; Mode - value that appears most often, M - median; AM - arithmetic mean; SD - standard deviation

### Table 2. The prevalence of perennial and seasonal, mild and moderate/severe, intermittent and persistent AR relative to the median level of serum interleukin 33 in the whole sample

| IL-33 level (pg/ml) | Allergic rhinitis/Alergijski rinitis |
|---------------------|------------------------------------|
| Nivo IL-33 (pg/ml)  | Perennial/Perenijalni               |
|                     | Seasonal/ Sezonski                  |
| > Median/> Medijana | 16                                 |
| ≤ Median≤ Medijana  | 17                                 |
| Mild/Blag          | 7                                  |
|                     | 8                                  |
| Intermittent/Intermitentni | 6                             |
| Persistent/Perzistentni | 4                             |

Legend: IL-33 - interleukin 33; Median – the median level in the whole sample

References:

Milanović B, et al. IL-33 in Children with Allergic Respiratory Diseases
The Table 3 shows the prevalence of examinees with a certain AR type (classified based on causal allergen type, duration and clinical severity) relative to the median serum interleukin-33 level in the whole sample. The results of the chi-square test showed that the difference among serum IL-33 levels in examinees with different AR types was not statistically significant ($\chi^2 = 4.44; p = 0.618; p > 0.05$).

**Table 3. The prevalence of certain AR types relative to the median serum interleukin-33 level**

| IL-33 level (pg/ml) Nivo IL-33 (pg/ml) | Allergic rhinitis/Alergijski rinitis |
|---------------------------------------|-------------------------------------|
| > Median/> Medijana                   | Perennial/Perenijalni               |
| ≤ Median/> Medijana                   | Seasonal/Sezonski                   |
| > Median/> Medijana                   | Mild/Blag                           |
| ≤ Median/> Medijana                   | Moderate/severe/Srednje težak/težak |
| > Median/> Medijana                   | Intermittent/Intermitentni          |
| ≤ Median/> Medijana                   | Persistent/Perzistentni             |

Legend: IL-33 - interleukin 33; Median - median level: 1 - intermittent + mild; 2 - intermittent + moderate/severe; 3 - persistent + mild; 4 - persistent + moderate/severe; a-seasonal; b-perennial.

**Discussion**

There was no significant difference between the control group of healthy examinees and the children with AA with/without AR in regard to the sex distribution, age, and obesity level. Out of the total number of children with AA, the majority of our examinees (85.25%) had normal weight. Also, in another similar study, children with AA mostly had normal weight [13]. A study which analyzed the relationship of IL-33 level and inflammation associated with obesity showed that activation of IL-33/ST2 axis had an anti-inflammatory role [14].

In our study, the average serum IL-33 level, in children with AA and with/without AR, was $2.550 \pm 3.587 \text{ pg/ml}$. A significantly higher average serum IL-33 level, compared to the level obtained in our examinees, was found in the study performed by Bahrami et al. and it was $15.17 \pm 32.3 \text{ pg/ml}$ [15]. This difference in the average serum IL-33 level in children with AA can be explained by different inclusion criteria of the examinees. In the study conducted by Bahrami et al., children were included regardless of the duration and severity of AA, unlike examinees in our study who had persistent, mild or moderate AA.

A study that included a series of adult examinees with AA detected higher serum IL-33 levels compared to our study. The study IL-33 level in adult examinees with a mild form of persistent AA was $202.6 \text{ pg/ml}$, while in patients with moderate AA it was $380.4 \text{ pg/ml}$. These differences in serum IL-33 levels may be due to the fact that the study included a series of adult patients with other allergic diseases besides AA. Also, in the afore-mentioned study, IL-33 levels were determined using a test which differs from the one used in our study in terms of sensitivity, standard range, minimal detectable level, and the manufacturer [16]. The difference in serum IL-33 levels between examinees included in our study and adult examinees can additionally be explained by the characteristics of our examinees. One of the exclusion criteria in our study was, among others (except for AR), presence of other allergic diseases which probably could affect serum IL-33 level. Also, it should not be neglected that our study included children, while the study by Momen et al. tested adult population.
The median level of serum IL-33 recorded in healthy children in our study was 0.573 ± 0.632 pg/ml and it is similar to median levels of IL-33 in other studies that included healthy pediatric population. For example, the median level of IL-33 in healthy children from an Iranian study was 0.61 ± 2.16 pg/ml [15]. A higher median level of IL-33 in healthy adult examinees in the mentioned study compared to the levels in healthy children in our study suggests that the age of examinees may be a significant factor in defining normal serum IL-33 level range, which is a common practice in most laboratory findings.

The results of our study show that serum IL-33 levels in children with AA and with/without AR are significantly higher compared to those in healthy children. Higher serum IL-33 levels in children with AA compared to healthy children were also detected in studies with a large number of examinees. Meta-analysis of eight earlier studies which included 330 children with AA and 248 healthy children also showed that serum IL-33 levels were higher in children with AA [17].

The study of Bahrami et al. also showed that serum IL-33 levels were significantly higher in children with AA compared to the control group of children [15]. Furthermore, studies with adults also show that patients with AA have significantly higher serum IL-33 levels compared to healthy examinees [16, 18].

The coexistence of AA and AR is common [19]. In our study, 39 (63.9%) children were diagnosed with AA and AR. Similarly, results of other studies that analyzed the coexistence of these two allergic diseases showed that AA is accompanied by AR in 30-80% of AR cases [20, 21].

The importance of IL-33 in AR pathogenesis is suggested by a study conducted in an animal experimental model of AR caused by ambrosia pollen which proved that mice with a removed IL-33 gene have a decreased production of Th2 cytokine as well as decreased accumulation of eosinophils, basophils and Th2 lymphocytes in nasal mucosa and lower frequency of sneezing [22].

The children in our study with both AA and AR had significantly higher serum IL-33 levels compared to children with AA only.

Similarly, a study by Bonanno et al. which compared serum IL-33 levels in examinees with AA and AR and examinees with AR only showed that IL-33 levels were significantly higher in examinees who had both of these two allergic diseases (AA and AR) [23].

The significance of IL-33 in the exacerbation of AR is indicated in a study with adult patients in which serum IL-33 levels were significantly higher in adult patients with AR sensitized to Japanese cedar pollen in the pollination season, when the pollen concentration in the air is highest, compared to the IL-33 levels measured out-of-the-pollination season [24].

In our study, children with higher serum IL-33 levels also had a more severe form of AA. These results are in accordance with the results of previous studies. Bahrami et al. showed that the lowest serum IL-33 levels were detected in children with mild AA, slightly higher in children with moderate AA, and the highest levels were identified in children with a severe form of AA [15]. The study including adult patients also showed that there was a significant difference among serum IL-33 levels in patients with mild, moderate and severe AA [17]. Guo et al. conducted a study including 45 adult patients and proved that there was a positive correlation between serum IL-33 level, thickening of the basal membrane in the bronchial biopsy samples, and AA severity [25].

The results of our study do not indicate that there is a difference among serum IL-33 levels in children with both AA and AR relative to causal allergen of AR (perennial, seasonal), AR severity (mild, moderate/severe) and AR duration (intermittent, persistent) as well as relative to different AR forms for which classification was done based on afore-mentioned AR features. However, a study by Yang et al. showed that the IL-33 levels in nasal secretion of patients with AR were significantly higher during the causal allergen-pollination season compared to those identified out of the pollination season [24]. A study performed by Asak et al. showed that examinees with severe AR have higher IL-33 levels of nasal secretion [26].

Similar values of serum IL-33 in children with different causal allergens, severity, duration, and AR forms are a possible consequence of serum IL-33 level detection independently of pollination season i.e. examinee exposure to the causal allergen. Measuring of serum IL-33 level was done independently of severity and earlier duration of AR at the moment of blood sample collection. Furthermore, all the children in our study group had both AR and AA.

Conclusion

The results of our study indicate that serum interleukin-33 levels in children with allergic respiratory diseases are significantly higher than in healthy children. Children who had both allergic asthma and allergic rhinitis had higher levels of this cytokine compared to children who had only allergic asthma. Patients with higher serum interleukin-33 levels also had more severe forms of allergic asthma. The causal allergen type, severity and duration of allergic rhinitis, i.e. different forms of allergic rhinitis did not significantly impact serum interleukin-33 levels in children with allergic asthma. The results confirm that interleukin-33 may be a potent inflammatory biomarker for the diagnosis of allergic respiratory diseases and suggest a potential importance of interleukin-33 correlating with allergic asthma severity and respiratory inflammatory process extension assessment. Importance of interleukin-33 correlating with allergic asthma severity and respiratory inflammatory process extension assessment.
Pregl. 2010;63(5-6):409-13. 

Jednodugi primene inhalatornih glikokortikosteroida. Med

Igrutinović Z. Indeks telesne mase dece sa astmom pre i posle

Immunol. 2010;126(3):466-76.

on asthma (ARIA) guidelines 2010. revision. J Allergy Clin

Canonica GW, Casale TB, et al. Allergic rhinitis and its impact

asthma. Lancet Respir Med. 2014;2(3):226-37.

Johnston SL. Role of interleukin 33 in respiratory allergy and

ecules. 2018;23(7):1665.

LX. Interleukin-33: its emerging role in allergic diseases. Mol

lergic diseases. Int J Mol Sci. 2019;20(23):31766607.

Puppo F, et al. IL-33/IL-31 axis in immune-mediated and al

almost, absent in many. Nat Rev Immunol. 2015;15(1):57-65.

flammation. 2019;16(1):251.

and severe neurodegeneration in retinal detachment. J Neuroin

mation in mice is mediated by group 2 innate lymphoid cells in

concert with basophils. J Invest Dermatol. 2019;139(10):2185-94.

Tahaghoghi-Hajghorbani S, Ajami A, Ghorbanalipoor S, Hosseini-Khaz H, Taghiloo S, Khaje-Enayati P, et al. Protective
effect of TSLP and IL-33 cytokines in ulcerative colitis. Auto

 Immun Highlights. 2019;10(1):1.

Hasan A, Kochumon S, Al-Ozairi E, Tuomilehto J, Ahmad R. Association between adipose tissue interleukin-33 and immunometabolic markers in individuals with varying degrees of glycemia. Dis Markers. 2019;2019:7901062.

Augustine J, Pavlou S, Ali I, Harkin K, Ozaki E, Campbell M, et al. IL-33 deficiency causes persistent inflammation and severe neurodegeneration in retinal detachment. J Neuroinflammation. 2019;16(1):251.

Fahy JV. Type 2 inflammation in asthma - present in most, absent in many. Nat Rev Immunol. 2015;15(1):57-65.

Murdaca G, Greco M, Tonacci A, Negrini S, Borro M, Puppo F, et al. IL-33/IL-31 axis in immune-mediated and allergic diseases. Int J Mol Sci. 2019;20(23):31766607.

Ding W, Zou GL, Zhang W, Lai XN, Chen HW, Xiong LX. Interleukin-33: its emerging role in allergic diseases. Molecules. 2018;23(7):1665.

Makrimioti H, Toussaint M, Jackson DJ, Walton RP, Johnston SL. Role of interleukin 33 in respiratory allergy and asthma. Lancet Respir Med. 2014;2(3):226-37.

Brožek JL, Bousquet J, Baena-Cagnani CE, Bonini S, Canonica GW, Casale TB, et al. Allergic rhinitis and its impact on asthma (ARIA) guidelines 2010. revision. J Allergy Clin Immunol. 2010;126(3):466-76.

Kostić G, Ilić N, Petrović M, Marković S, Vuletić B, Igrutinović Z. Indeks telesne mase dece sa astmom pre i posle jednogodišnje primene inhalatornih glikokortikosteroida. Med Pregl. 2010;63(5-6):409-13.

Rad je priimenj en. 8. IV 2020.

Recenziran 27. IV 2020.

Prihvaćen za štampu 20. V 2020.

References

1. Global Initiative for Asthma (GINA). 2018 GINA report, global strategy for asthma management and prevention [Internet]. 2018 [updated 2018; cited 2020 Mar 15]. Available from: https://ginasthma.org/wp-content/uploads/2019/01/2018-GINA.pdf.

2. Soriano JB, Abajobir AA, Abate KH, Abera SF, Agrawal A, Ahmed MB, et al. Global, regional, and national deaths, prevalence, disability-adjusted life years, and years lived with disability for chronic obstructive pulmonary disease and asthma, 1990-2015: a systematic analysis for the Global Burden of Disease Study 2015. Lancet Respir Med. 2017;5(9):691-706.

3. Bush A. Pathophysiological mechanisms of asthma. Front Pediatr. 2019;7:68.

4. Imai Y, Yasuda K, Nagai M, Kusakabe M, Kubo M, Nakashiki K, et al. IL-33-induced atopic dermatitis-like inflammation in mice is mediated by group 2 innate lymphoid cells in concert with basophils. J Invest Dermatol. 2019;139(10):2185-94.

5. Tahaghoghi-Hajghorbani S, Ajami A, Ghorbanalipoor S, Hosseini-Khaz H, Taghiloo S, Khaje-Enayati P, et al. Protective effect of TSLP and IL-33 cytokines in ulcerative colitis. Auto Immun Highlights. 2019;10(1):1.

6. Hasan A, Kochumon S, Al-Ozairi E, Tuomilehto J, Ahmad R. Association between adipose tissue interleukin-33 and immunometabolic markers in individuals with varying degrees of glycemia. Dis Markers. 2019;2019:7901062.

7. Augustine J, Pavlou S, Ali I, Harkin K, Ozaki E, Campbell M, et al. IL-33 deficiency causes persistent inflammation and severe neurodegeneration in retinal detachment. J Neuroinflammation. 2019;16(1):251.

8. Fahy JV. Type 2 inflammation in asthma - present in most, absent in many. Nat Rev Immunol. 2015;15(1):57-65.

9. Murdaca G, Greco M, Tonacci A, Negrini S, Borro M, Puppo F, et al. IL-33/IL-31 axis in immune-mediated and allergic diseases. Int J Mol Sci. 2019;20(23):31766607.

10. Ding W, Zou GL, Zhang W, Lai XN, Chen HW, Xiong LX. Interleukin-33: its emerging role in allergic diseases. Molecules. 2018;23(7):1665.

11. Makrimioti H, Toussaint M, Jackson DJ, Walton RP, Johnston SL. Role of interleukin 33 in respiratory allergy and asthma. Lancet Respir Med. 2014;2(3):226-37.

12. Brožek JL, Bousquet J, Baena-Cagnani CE, Bonini S, Canonica GW, Casale TB, et al. Allergic rhinitis and its impact on asthma (ARIA) guidelines 2010. revision. J Allergy Clin Immunol. 2010;126(3):466-76.

13. Kostić G, Ilić N, Petrović M, Marković S, Vuletić B, Igrutinović Z. Indeks telesne mase dece sa astmom pre i posle jednogodišnje primene inhalatornih glikokortikosteroida. Med Pregl. 2010;63(5-6):409-13.