SERUM INTERLEUKIN-33 LEVELS ARE ELEVATED BUT NOT ASSOCIATED WITH DISEASE ACTIVITY IN PATIENTS WITH RHEUMATOID ARTHRITIS

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ABSTRACT

Introduction: *Interleukin (IL)-33 is a new member of the IL-1 superfamily. After cellular damage, IL-33 is released into the extracellular space and functions as an alarmin to induce the innate immunity. Recent studies suggest that IL-33 can also induce T helper-1 (Th1), Th2 and Th17 mediated adaptive immune responses. So, as a pro-inflammatory cytokine, IL-33 plays an important role in the pathogenesis of autoimmune and inflammatory diseases. In this recpect, we also assessed the effect of serum IL-33 level in rheumatoid arthritis (RA) and ankylosing spondylitis (AS) which are the most common inflammatory arthritis.*

Materials and methods*: Thirty RA patients, 30 AS patients, and 30 healthy controls were recruited. Blood samples were obtained for detecting serum IL-33 levels. The disease activity was assessed with diseases activity score-28 in RA patients and with the Bath ankylosing spondylitis disease activity index in AS patients. All patients were evaluated for severity of pain, fatigue, the physicians's global assessment and the patient's global assessment. Morning stiffness was evaluated in minutes. Functional status of the all patients were evaluated with the health assesment questionnaire. Patients with AS were also assessed with the Bath ankylosing spondylitis functional index. Relationship between serum IL-33 levels and disease activity parameters were assessed.*

Results*: Serum IL-33 levels were higher in RA patients than in AS patients and healthy controls. Increased serum levels of IL-33 were not correlated with the disease activity parameters in RA patients. There was no significant relationship between serum IL-33 levels and rheumatoid factor or anti-cyclic citrullinated peptide antibody levels in RA patients. Serum IL-33 levels were not significantly different in patients with AS and healthy conrols.*

Conclusion*: Serum IL-33 levels were higher in patients with RA than in patients with AS and healthy controls. But serum IL-33 level was not associated with the disease activity, this result may be due to the cross-sectional design of the study. A better understanding the pathogenesis of diseases is important to develop new therapeutic agents. Our study suggest that IL-33 may have a complex role in the pathogenesis of RA and may be a promising target for the treatment of RA. But larger follow-up studies are needed to support this opinion.*

Keywords: *Ankylosing spondylitis, Disease activity, Interleukin, IL-33, Rheumatoid arthritis.*

DOI: 10.19193/0393-6384_2020_6_521

Received *April 30, 2020;* ***Accepted*** *August 20, 2020*

Introduction

Interleukin (IL)-33 is a new member of the IL-1 family, and exerts its functions via the transmembrane form of the suppressor of tumorigenicity 2 (ST2) receptor, which is commonly expressed on CD4+ T cells, CD8+ T cells, B cells, mast cells, macrophages, neutrophils, eosinophils, basophils, natural killer cells, and group 2 innate lymphoid cells[(1)].

In recent years, IL-33 became a focus of many studies due to its possible role in autoimmune and inflammatory diseases. IL-33 has been originally described as a potent inducer of mast cells and T helper-2 (Th2) cells. Therefore, it has attracted a lot of interest as a potential therapeutic target in asthma and other allergic diseases. However, later studies indicated that IL-33/ST2 signaling also plays an important role to induce Th1 and Th17 mediated immune responses[(1,2)].

Serum levels of IL-33 and its soluble ST2 receptor (sST2) have been reported to be up-regulated in various Th1 and Th17-mediated autoimmune diseases, such as rheumatoid arthritis (RA), ankylosing spondylitis (AS), psoriasis, inflammatory bowel diseases, autoimmune hepatitis, type 1 diabetes and multiple sclerosis[3-5]. So, IL-33 may also be a promising therapeutic target for the treatment of those autoimmune diseases mediated by Th1 and Th17. But, there are a few and conflicting clinical trials on the effect of IL-33 in RA and AS. Hereby, we also investigated the serum level of IL-33 and its relationship with disease activity in patients with RA and AS.

Materials and methods

This cross-sectional case-control study included 30 patients with RA (23 females, 7 males; mean age 53.5±13.2 years) and 30 patients with AS (13 females, 17 males; mean age 40.0±10.9 years). 30 healthy controls (22 females, 8 males; mean age 47.6±15.6 years) were also included. The diagnosis of RA was based on the American College of Rheumatology criteria revised in 1987[6]. Patients were diagnosed as having AS if they met the modified New York criteria[7]. Patients with any known autoimmune disease other than RA and AS, those with acute or chronic infections, malingnancies, known severe lung, liver, and kidney diseases, endocrinological or neurological diseases were excluded from the study.

This study was performed in accordance with the ethical guidelines of 1964 Declaration of Helsinki and its later amendments. Local Ethics Committee approved the study and written informed consent was obtained from all patients and controls. All participants agreed to undergo blood testing and have their blood stored for future research.

Clinical assessments

Medical history and medications were optained from all patients with RA and AS. Using the visual analogue scale (VAS) (0-100 mm), all patients were evaluated for severity of pain, fatigue, the physicians's global assessment and the patient's global assessment. Morning stiffness was evaluated in minutes. Functional status of all patients were evaluated with the health assesment questionnaire (HAQ)[9]. The disease activity was assessed with the Diseases Activity Score-28 (DAS-28) in RA patients and with the Bath Ankylosing Spondylitis Disease Activity Index (BASDAI) in AS patients[9,10].

Patients with RA were divided into two subgroups: low disease activity (DAS-28 ≤3.2) and moderate/high disease activity (DAS-28 >3.2). Similarly, patients with AS were divided into two subgroups: low disease activity (BASDAI<4) and high disease activity (BASDAI ≥4). Patients with AS were also assessed with the Bath Ankylosing Spondylitis Functional Index (BASFI) in terms of their functional condition[11].

Laboratory assessments

All participants underwent routine laboratory evaluations consisted of erythrocyte sedimentation rate (ESR), C-reactive protein (CRP) level, complete blood count, blood biochemistry and urine analyses. In patients with RA, rheumatoid factor (RF) and anti-cyclic citrullinated peptide (anti-CCP) antibody levels were measured with the nephalometric method and enzyme-linked immunosorbent assay (ELISA), respectively. Blood samples of all patients and healthy controls were collected in citrated tubes and centrifuged for 15 minutes at 2000 rpm. The obtained serum samples were stored at -80°C untill analysis. Serum IL-33 levels were detected by ELISA using the commercially available kits (EastBiopharm, China) according to the manufacturer's protocol. Intra- and inter-assay variability percentages for IL-33 were <10% and <12%, respectively.

Statistical analysis

In comparisons between groups, chi-square test was used for categorical variables and independent t-test was used for continous variables. Mann-Whitney U test was used for the comparison of continous variables that did not show normal distribution. Correlations of serum IL-33 levels with other variables were analyzed using Spearman's correlation test. All statistical analyses were performed by SPSS 15.0 program. P <0.05 was accepted statistically significant.

Results

Clinical and laboratory characteristics of patients with RA and AS, and their comparisons with those of healthy controls are given in Table 1. The mean age and gender distribution were similar between RA patients and healthy controls. Although gender distribution was similar between the AS group and the control group mean age was significantly lower in the AS group (p=0.018). The mean disease duration in the patient groups with RA and AS

was 9.5±6.2 years and 6.1±4.8 years, respectively. Mean ESR and CRP values in RA patients were signicicantly higher than healthy controls (p<0.0001 and p=0.040, respectively, Table 1). There was no significant difference between patients with AS and healthy controls in terms of mean ESR and CRP values.

	RA (N=30)	AS (N=30)	Controls (N=30)	P[a]	P[b]
Age (year)	53,5±13,2 (32-91)	40,0±10,9 (22-68)	47,6±15,6 (15-77)	0,173	0,018*
Female, N(%)	23(76,7)	13(43,3)	22(73,3)	0,167	0,213
Disease duration (year)	9,5±6,2 (1-22)	6,1±4,8 (1-21)	-	-	-
Pain (0-100 mm VAS)	46,6±24,1 (10-90)	42,8±18,4 (20-90)	-	-	-
Morning stiffness (minute)	51±40,3 (0-120)	62,8±41,5 (0-120)	-	-	-
CRP (g/dL)	8,9±15,1 (0-73)	6,2±11,0 (0-55)	2,3±2,2 (0-8)	0,040*	0,302
ESR (mm/h)	41,2±27.4 (1-97)	21,6±18,3 (3-67)	13,5±7,9 (2-30)	0,000*	0,195
RF (IU/mL)	87,7±110,1 (6-588)	-	8,4±64,7 (0-361)	0,000*	-
Anti-CCP (U/mL)	266,4±366,1 (3,7-1000)	-	14,5±9,4 (2,5-46,6)	0,000*	-
IL-33 (pg/mL)	414.21±592.36 (7.23-1929.22)	171.21±325.07 (20.01-1289.9)	123.75±169.63 (6.33-721.58)	0.024*	0.824
HAQ (0-3)	1,2±0,7 (10,3-2,60)	2,5±6,1 (0,25-2,6)	-	-	-
DAS-28 (0-9,4)	4,5±2,0 (1,28-7,94)	-	-	-	-
BASDAI (0-10)	-	4,1±2,0 (1,2-10)	-	-	-
BASFI (0-10)	-	3,8±2,1 (1-10)	-	-	-

Table 1: Clinical and laboratory characteristics of patients with rheumatoid arthritis and ankylosing spondylitis, and their comparisons with those of healthy controls.
*Values are presented as mean±standard deviation (range). *Statistically significant results (p<0.05), [a]Comparison between RA and controls, bComparison between AS and controls, VAS: Visual Analog Scale, CRP: C-Reactive Protein, ESR: Erythrocyte Sedimentation Rate, RF: Rheumatoid Factor, Anti-CCP: Anti-Cyclic Citrullinated Peptide, IL: Interleukin, HAQ: Health Assessment Questionnaire, DAS: Disease Activity Score, BASDAI: Bath Ankylosing Spondylitis Disease Activity Index, BASFI: Bath Ankylosing Spondylitis Functional Index.*

	IL-33	
	P	**R**
Morning stiffness	0.455	0.142
Pain	0.074	0.331
ESH	0.197	0.242
CRP	0.230	0.226
RF	0.159	0.264
Anti-CCP	0.516	0.123
DAS-28	0.216	0.232
HAQ	0.547	0.115

Table 2: Spearman's correlation coefficients (r) for serum IL-33 levels and various clinical and laboratory parameters in patients with rheumatoid arthritis.
IL: Interleukin, ESR: Erythrocyte Sedimentation Rate, CRP: C-Reactive Protein, RF: Rheumatoid Factor, Anti-CCP: Anti-Cyclic Citrullinated Peptide, DAS: Disease Activity Score, HAQ: Health Assessment Questionnaire

In the RA group, eight (26.6%) patients were being treated with methotrexate monotherapy, 12 (40%) patients with methotrexate plus prednisolone, three (10%) patients with methotrexate plus hydroxychloroquine, and seven (23.3%) patients with leflunomide plus prednisolone. None of the patients with RA had administered any kind of anti-tumor necrosis factor-alpha (anti-TNF-α) therapy. In the AS group, seven (23.3%) patients were on non-steroidal anti-inflammatory drug (NSAID) monotherapy, nine (30%) patients on sulfasalazine plus NSAID, and 14 (46.7%) patients on anti-TNF-α therapy.

Serum IL-33 levels were significantly higher in RA patients compared to healthy controls (p=0,024, Table 1). Moreover, serum IL-33 levels in patients with RA were also significantly higher than in patients with AS (p=0.012). But, there was no significant correlation between serum IL-33 levels and clinical and laboratory parameters showing disease activity in RA patients (Table 2). Similarly, no significant difference was observed in serum IL-33 levels between low disease activity and moderate/high disease activity subgroups of RA patients (p=0,175).

In the comparison between AS patients and healthy controls, serum IL-33 levels were not found significantly different (p=0.824, Table 1). When low disease activity and high disease activity subgroups of AS patients were compared, no significant difference was observed in serum IL-33 levels (p=0.625).

Similarly, there was no significant correlation between serum IL-33 levels and disease activity parameters in AS patients (Table 3). Moreover, serum IL-33 levels were similar when compared to 14 AS

	IL-33	
	P	R
Morning stiffness	0.424	0.152
Pain	0.525	0.121
ESH	0.063	0.344
CRP	0.560	0.111
BASDAI	0.833	0.040
BASFI	0.806	0.047
HAQ	0.278	0.205

Table 3: Spearman's correlation coefficients (**r**) for serum IL-33 levels and various clinical and laboratory parameters in patients with ankylosing spondylitis.
IL: Interleukin, ESR: Erythrocyte Sedimentation Rate, CRP: C-Reactive Protein, BASDAI: Bath Ankylosing Spondylitis Disease Activity Index, BASFI: Bath Ankylosing Spondylitis Functional Index, HAQ: Health Assessment Questionnaire.

patients using anti-TNF-α therapy and 16 AS patients without anti-TNF-α therapy (p = 0.189).

Discussion

This study aimed to investigate the level of serum IL-33 in patients with RA and AS and its association with the activity of diseases. Serum IL-33 levels in patients with RA were significantly higher than both healthy controls and AS patients. But, serum IL-33 level was not different from healthy controls in patients with AS.

In addition, there was no relationship between the disease activity and serum IL-33 levels in both RA and AS patients.

IL-33 have important functions in both innate and adaptive immunity. This cytokine is an alarmin and expressed in the nucleus of endothelial and epithelial cells of barrier tissues as well as various immune cells. When the cells are activated or damaged, it is released to extracellular space and alerts the immune system[1]. As an alarmin, IL-33 has anti-bacterial, anti-viral, anti-parasitic and anti-tumoral effects via recruitment of CD8(+) T cells, natural killer cells, γδ T cells, macrophages, neutrophils and eosinophils[12]. Additionally, IL-33 is a proinflammatory cytokine and plays a critical role in adaptive immunity activating antigen presenting dendritic cells and macrophages, T and B cells as well as mast cells. Interestingly, IL-33 has also been shown to have immunoregulatory effect by activating regulatory T cells (Treg). So, it mediates anti-inflammatory and tissue-protective functions during the recovery phase following tissue injury, especially in the central nervous system and gastrointestinal system[2,13].

Because of proinflammatory activity, IL-33 has been investigated in the pathogenesis of autoimmune and inflammatory diseases. Elevated levels of serum IL-33 were initially reported especially in asthma and allergic diseases. Later, increased IL-33 levels have been reported in many autoimmune and inflammatory diseases, such as psoriasis, inflammatory bowel diseases, autoimmune hepatitis, systemic lupus erythematosus, systemic sclerosis, Sjögren's syndrome, dermatomyositis, Behçet's disease, RA, and AS[4,14-16].

In this study, we found that serum IL-33 levels are increased in patiensts with RA. Similar to our result, previous studies have reported that serum and synovial fluid levels of IL-33 are elevated in patients with RA[17-19]. Notably, in some studies, serum and/or synovial fluid levels of IL-33 were positively correlated with disease activity in patients with RA[17,18,20]. Kageyama et al.[20] reported that serum IL-33 levels showed a significant correlation with the number of tender joints, CRP, and DAS28 in patients with RA. In their study, the mean serum IL-33 level decreased significantly at 3 months with etanercept treatment. Matsuyama et al.[17] found that serum IL-33 levels were significantly higher in RA patients, especially in the high disease activity group compared to the moderate or low disease activity group. A positive correlation between serum IL-33 levels to DAS28 was observed. The number of painful and swollen joints was also highest in the group positive for serum IL-33. In a study of 120 RA patients, the level of synovial fluid IL-33 was significantly higher in RA than in osteoarthritis, which was also correlated with DAS-28, ESR, RF, as well as the level of serum IL-33[18]. In a previous study, the change of serum IL-33 level following the anti-TNF-α therapy was tested in 40 RA patients. The level of serum IL-33 was positively correlated with the disease activity and serum IL-33 levels significantly decreased after anti-TNF-α therapy[19]. Shen et al.[21] showed that baseline serum IL-33 levels were associated with DAS28, ESR and serum TNF-α levels. In their study, detectable serum IL-33 level was an independent predictor for carotid plaque progression in RA patients. So, they proposed that inflammation induced by IL-33 may play a significant role in the development of cardiovascular disease in RA. In our study, there was no association with the disease activity and serum IL-33 levels in patients with RA. Similar to our results, Xiangyang et al.[22] did not find any correlation between serum IL-33 levels and other clinical parameters, such as DAS28, ESR and CRP. In another study, serum IL-33 levels were higher in RA patients than controls, but not correlated with disease activity parameters such as DAS28, ESR and CRP[19]. This may reflect a complex relationship of serum IL-33 levels with the inflammation in patients with RA. Perhaps, drug therapy may have partially affected our results. In a previous study, treatment with conventional disease modifying anti-rheumatic drugs reduced the IL-33 level as well as the inflammation in 10 treatment-naive RA patients[23]. Increased serum IL-33 levels could be a possible biomarker to reflect the potential risks of bone erosion and osteoporosis. An experimental arthritis model indicated that IL-33 treatment notably increases mononuclear and polymorphonuclear cell infiltration into the joints, with synovial hyperplasia, cartilage damage, and bone erosion[24]. In addition, stimulation of fibroblast-like

synoviocytes from RA patients with IL-33 induced receptor activator of nuclear factors-kappa B ligand (RANKL) expression and osteoclastogenesis[25]. In a study involving 121 patients with RA, there was a positive correlation between the serum IL-33 level and joint damage assessed by the modified Sharp Score[22].

IL-33 might be involved in the production of RF and anti-CCP antibodies in RA patients. Serum IL-33 levels were found positively correlated with RF and anti-CCP antibody levels in previous studies[18,19,22,26]. Additionally, it has been suggested that the presence of detectable serum IL-33 is associated with good response to rituximab as well as the presence of RF or anti-CCP antibodies[27]). Conversely, a recent study found that the detectable level of serum IL-33 is associated with RF and/or anti-CCP positivity but is not a predictive marker for response to rituximab or TNF-α inhibitors in RA patients[26]. In our study, the level of serum IL-33 was not correlated with the level of RF or anti-CCP antibodies in RA patients.

Previous studies reported that the synovial fluid level of IL-33 was significantly higher in patients with RA than in patients with osteoarthritis[17,23,28]. It has been shown that synovial fibroblasts of RA patients produce a significant amount of IL-33. IL-33 may exacerbate the inflammation by abundantly producing TNF-α, IL-1, IL6 and IL8 from synovial mast cells[17,29].

IL-33 is also implicated in the pathogenesis of AS with the effect of promoting TNF-α and IL-17 productions[30]. Previous studies have found that serum IL-33 levels are elevated in patients with AS compared to healthy controls[30,31]. In a study involving 140 AS patients, serum IL-33 levels were found higher in the patients than in healthy controls and significantly correlated with the BASDAI. Elevated levels of IL-33 were especially detected in the patients with peripheral arthritis, and eye involvement[31]. Han et al.[30] repoted that serum levels of IL-33 were elevated in AS patients. In their study, IL-33 levels in serum were positively correlated with TNF-α and IL-17 levels as well as BASDAI. Similarly, another study indicated that serum IL-33 levels were increased and significantly higher in patients with active AS than in those with inactive AS. Additionally, they found that serum IL-33 levels were correlated with CRP and BASDAI, but did not with ESR[32].

All of these studies mentioned above suggests that serum levels of IL-33 could partially reflect the disease activity and indicate that IL-33 may play an important role in the pathogenesis of AS. But in our study serum IL-33 levels were not different between AS patients and healthy conrols. This may be due to the small sample size in this study. Another possibility, about half of the our AS patients were receiving anti-TNF-α therapy, so serum IL-33 levels may have been reduced to near normal levels. This presumption could be supported by the recently published data that serum levels of IL-33 were reduced after anti-TNF therapy in psoriasis, ulcerative colitis, as well as in RA patients[4,19,33]. Previous studies either did not include AS patients on anti-TNF-α therapy[30] or did not mention the treatments received[32].

A better understanding the pathogenesis of autoimmune diseases is important to develop new therapeutic agents. In this study, although it was not associated with disease activity, the serum IL-33 level was found to be higher in RA patients than in healthy controls, as well as in AS patients. So, IL-33 may be involved in the pathogenesis of RA. We did not find any difference in serum IL 33 levels between AS patients and healthy controls. Because this study was cross-sectional and performed with a small number of patients, these results should be confirmed in larger follow-up studies.

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