

Assessment of Interleukin-33 Levels in Patients with Familial Mediterranean Fever

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Abstract. Background: This study was designed to evaluate the relationship between serum interleukin-33 (IL-33) levels and clinical features of the disease in patients with Familial Mediterranean Fever (FMF). **Methods:** Fifty-four patients diagnosed with FMF (28 colchicine responsive and 26 colchicine resistant) and 29 healthy controls constituted the study population. Demographic, clinical, biochemical and inflammatory parameters, as well as serum IL-33 levels of the participants, were compared. **Results:** The mean age of FMF patients was 34.3 ± 9.8 years, and 54% were female. Colchicine-resistant patients exhibited significantly higher median CRP levels than both colchicine-responsive patients and healthy controls (median [IQR]: 16 [30.4] mg/L, 2.9 [3.4] mg/L, and 3.4 [2.8] mg/L, respectively; $p < 0.001$). Median serum IL-33 levels were higher in FMF patients than in controls (273 [387] ng/L vs. 221 [179] ng/L, $p = 0.06$). The colchicine-responsive group had significantly higher IL-33 levels compared to the control group (287 [495] ng/L vs. 221 [179] ng/L, $p = 0.006$), while no significant difference was observed between the colchicine-resistant group and controls (257 [219] ng/L vs. 221 [179] ng/L, $p = 0.74$). No significant correlations were identified between IL-33 levels and inflammatory markers or clinical characteristics. **Conclusions:** Serum IL-33 levels do not seem to be associated with FMF disease activity; however, the observed increase in colchicine-responsive patients may indicate an immunomodulatory or compensatory function. Further comprehensive studies are needed to elucidate the role of IL-33 in FMF pathogenesis.

Keywords: autoinflammatory diseases, colchicine, cytokine, familial mediterranean fever, interleukin-33.

What is new? What is important?

Serum IL-33 levels were found to be significantly higher in colchicine-responsive FMF patients compared with healthy controls. The increase observed in colchicine-responsive patients suggests that IL-33 may be associated with regulatory components of the immune response rather than reflecting active inflammation during the attack-free period of FMF. Our study provides a different perspective on IL-33 cytokine biology in FMF and indicates that IL-33-related pathways should be evaluated using more detailed mechanistic approaches.

INTRODUCTION

FMF is defined as an autoinflammatory syndrome involving periodic episodes of fever, inflammation of serous membranes, arthritis, and erysipelas-like erythema [1]. It is recognized as the most widespread monogenic autoinflammatory disorder, mainly observed among individuals of Turkish, Armenian, Jewish, and Arab descent [2]. The underlying cause of the disease is mutations in

the MEFV gene, the gene that encodes pyrin. Mutant pyrin leads to excessive activation of caspase-1, thereby causing overproduction of interleukin-1 β (IL-1 β), IL-18, and Gasdermin D. IL-1 β has been identified as the major cytokine underlying the clinical manifestations of the disease [1]. In this context, cytokines of the IL-1 family are considered to have a central role in the pathogenesis of FMF. This cytokine family comprises a diverse group of mediators with both

proinflammatory and anti-inflammatory functions. One of the best-defined members of this family, IL-1 β , has a critical role in fever response and immune system activation. Other members of the family include IL-33, IL-18, and IL-36 [3].

IL-33, an IL-1 family cytokine with nuclear localization, is implicated in the regulation of tissue homeostasis and inflammatory responses [4]. IL-33 exerts its effects through its specific receptor ST2 (Suppression of Tumorigenicity 2, also known as IL1RL1/Interleukin-1 Receptor Like 1, a toll-like receptor from the IL-1 receptor family); after binding to ST2, it interacts with the co-receptor IL-1RAcP (interleukin-1 receptor accessory protein), thereby activating intracellular signaling pathways and initiating its inflammatory effects [5]. IL-33 has critical roles in various pathological processes including infection, allergy, autoimmunity and cancer, by exhibiting dual effects ranging from proinflammatory responses to immune modulation, depending on the target immune cell type and microenvironmental signals [6].

The function of IL-33 was initially described in allergic asthma, and subsequently, numerous studies have demonstrated its important effects on various rheumatic diseases [7–9]. A recent study has demonstrated that a deletion carriage in the IL1RL1 gene was detected in more than 19% of patients with FMF, whereas no carriage was observed in the control group [10]. A possible contribution of IL-33 to the pathogenesis and clinical manifestations of FMF is suggested by these findings. However, the association between IL-33 and the clinical, laboratory, and therapeutic characteristics of FMF has been insufficiently investigated [11,12].

In this study, we aimed to investigate the association between serum IL-33 levels and clinical and laboratory parameters in FMF patients.

MATERIALS AND METHODS

This cross-sectional analysis evaluated 54 patients with FMF followed at a rheumatology clinic, along with 29 healthy individuals. Patient eligibility criteria included an age range of 18–65 years, a confirmed diagnosis of FMF based on the Tel Hashomer criteria [13], absence of concomitant inflammatory diseases, and provision of informed consent. Patients who were receiving treatments other than colchicine and any form of immunosuppressive therapy for other reasons were not included in the study.

The severity of FMF was evaluated using the International Severity Score for FMF (ISSF) [14]. The ISSF is a composite scoring system comprising nine clinical items, yielding a total score ranging from 0 to 10. A certain score is assigned to patients for each clinical criterion present; the total score of all criteria determines the disease severity. Based on the total ISSF score, disease severity was categorized as mild (0–2), moderate (3–5), or severe (≥ 6).

Participants were divided into three groups: healthy participants defined as group 1; colchicine-responsive FMF patients (those who had fewer than one attack in the last 6 months and had no persistent elevation in acute-phase reactants between attacks) defined as group 2 and FMF patients with colchicine-resistant disease (crFMF) defined as group 3. Colchicine-resistant FMF was defined as ongoing disease activity despite at least six months of treatment with the maximum tolerated dose of colchicine, characterized by a mean frequency of one or more attacks per month over the preceding three months and/or sustained elevation of acute-phase reactants between attacks [15,16].

The healthy control group consisted of individuals who presented to the check-up outpatient clinic and were invited to participate voluntarily. Eligibility required the absence of an FMF diagnosis or a history of FMF-related symptoms in the participants and their families. Individuals with known chronic inflammatory/autoimmune disease, acute infection (within the past week), malignancy, pregnancy/lactation, chronic kidney or liver disease, or current use of immunomodulatory/immunosuppressive therapy were not included in the control group. Control participants were screened through a brief clinical evaluation, and those with biochemical test results and CRP/ erythrocyte sedimentation rate (ESR) levels within the normal range were included. The control group was selected to match the age and sex distribution of the overall patient cohort.

Laboratory assessments included complete blood count, albumin, creatinine, ESR and CRP. For the measurement of serum IL-33 levels, fasting blood samples were collected during attack-free periods. IL-33 was assessed using a commercial Enzyme-Linked Immunosorbent Assay (ELISA) kit (Bioassay Technology Laboratory), with a working range of 10 ng/L – 2000 ng/L and sensitivity of 5.36 ng/L.

The study protocol adhered to the ethical principles of the Declaration of Helsinki and

complied with relevant institutional and national regulations. Ethical approval was obtained from the institutional ethics committee (Decision no: 769). All participants provided written informed consent before inclusion in the study.

STATISTICAL ANALYSIS

Statistical analyses were performed using SPSS version 21.0 (Chicago, IL, USA). Continuous variables were reported as mean $\pm$ standard deviation (SD) for normally distributed data and as median (interquartile range [IQR]) for non-normally distributed data, as appropriate. Normality was assessed using the Kolmogorov–Smirnov test and visual inspection of the distribution. Between-group comparisons were performed using the Kruskal–Wallis test; Dunn’s post hoc test was applied for pairwise subgroup comparisons. The Holm correction was used to reduce the accumulation of type I errors in multiple pairwise comparisons. Correlation analyses were assessed using Pearson’s or Spearman’s

correlation coefficients, as appropriate. For the study’s primary endpoint, serum IL-33 levels, effect sizes, and 95% confidence intervals were additionally reported for pairwise comparisons. A p-value <0.05 was considered statistically significant.

RESULTS

The study population consisted of 29 healthy controls and 54 patients with FMF, of whom 28 were classified as colchicine-responsive and 26 as colchicine-resistant. The mean age was 33.3 ± 11 years in the colchicine-responsive group and 35.4 ± 7 years in the colchicine-resistant group. Among the FMF patients, 54% were female and 46% were male. A higher proportion of females was noted among colchicine-responsive patients, while males were more common in the colchicine-resistant group ($p = 0.007$). Clinical and treatment characteristics of the patients are summarized in Table 1.

Table 1

Demographic data and disease characteristics

	Colchicine responsive FMF n=28	Colchicine resistant FMF n=26	P
Age, mean $\pm$ SD, years	33.3 $\pm$ 11.4	35.4 $\pm$ 7.6	0.44
Sex, female, n (%)	20 (71%)	9 (35%)	0.007
Age at disease onset, years	21 [12]	21.5 [15.25]	0.71
Duration of disease, years	9 [7]	15 [9]	0.005
Fever, n (%)	16 (57%)	19 (73%)	0.22
Abdominal pain, n (%)	20 (71%)	23 (88%)	0.12
Chest pain, n (%)	14 (50%)	13 (50%)	1.00
Arthritis, n (%)	18 (64%)	19 (73%)	0.48
Skin rash, n (%)	6 (21%)	7 (26%)	0.63
Myalgia, n (%)	10 (35%)	14 (53%)	0.18
Disease severity, ISSF			<0.001
Mild	23 (82%)	2 (8%)	
Moderate	5 (18%)	19 (73%)	
Severe	0 (0%)	5 (19%)	
Colchicine dose, mg/day	1 [0.5]	1.5 [1]	0.22

Note: All values are presented as mean $\pm$ or median [IQR] or percentage.

The presence of attacks defined in patients in remission indicates attacks in the pre-remission period.

Inflammatory markers, ESR and CRP were remarkably higher in the colchicine-resistant group compared to the control group ($p = 0.002$ and < 0.001 , respectively). Both ESR and CRP levels were significantly higher in the colchicine-resistant group compared with the colchicine-responsive group (ESR 22 [26.8] mm/h vs. 13 [11.3] mm/h, $p=0.001$, CRP 16 [30.5] mg/L, vs. 2.9 [3.4] mg/L, $p < 0.001$).

Median serum IL-33 levels were higher in FMF group compared to healthy control group (273 [387] ng/L vs 221 [179] ng/L, $p = 0.06$). The median serum IL-33 levels were significantly higher in the colchicine-responsive group compared to the control group (287 [495] ng/L vs 221 [179] ng/L, $p = 0.006$), (Table 2A). For pairwise comparisons of IL-33, Holm correction was applied; the adjusted p-values, effect sizes (r), and 95% confidence intervals are presented in Table 2B.

Table 2A

Comparison of laboratory parameters between groups

	Healthy Controls n=29	Colchicine responsive FMF n=28	Colchicine resistant FMF n=26	p1	p2	p3
Leukocyte, mm ³	6340 [2680]	7840 [2400]	7670 [2287]	0.11	0.18	0.97
Neutrophil, mm ³	3730 [1830]	4290 [2022]	4435 [2602]	0.20	0.14	0.67
Lymphocyte, mm ³	2220 [925]	2230 [752]	2010 [970]	0.40	0.16	0.03
Hemoglobin, g/dL	14.1 ± 1.8	13.5 ± 2.0	13.4 ± 2.1	0.29	0.24	0.87
Thrombocyte, x10 ³ /μL	255 [75]	275 [99]	276 [114]	0.17	0.38	0.84
Creatinine, mg/dL	0.75 [0.23]	0.68 [0.25]	0.82 [4.42]	0.05	0.20	0.02
Albumin, g/dL	4.61 ± 0.32	4.62 ± 0.29	4.29 ± 0.52	0.89	0.008	0.006
ESR, mm/h	14 [8.50]	13 [11.25]	22 [26.75]	0.57	0.002	0.001
CRP, mg/L	3.40 [2.75]	2.90 [3.35]	16 [30.48]	0.18	<0.001	<0.001
IL-33, ng/L	221 [179]	287 [495]	257 [219]	0.006	0.74	0.09

Note: p1: healthy control vs. colchicine-responsive, p2: healthy control vs. colchicine-resistant, p3: colchicine-responsive vs. colchicine-resistant

Values are given as mean +/- SD or median [IQR]

CRP: C-reactive protein, ESR: erythrocyte sedimentation rate, IL-33: interleukin 33

Table 2B

Pairwise comparisons for IL-33 with Holm-adjusted p-values, effect size r and 95% CI

	n1	n2	Z	p (2-tailed)	Holm p	r (95% CI)
Control vs. Responsive	29	28	-2.754	0.006	0.018	0.365 (0.115–0.571)
Control vs. Resistant	29	26	-0.329	0.742	0.742	0.044 (-0.224–0.306)
Responsive vs. Resistant	28	26	-1.688	0.091	0.182	0.230 (-0.041–0.469)

Note: r was calculated as $|Z|/\sqrt{N}$; 95% CI was estimated using Fisher's z

Serum IL-33 levels were not found to be significantly associated with clinical features. There was no statistically significant correlation between serum IL-33 levels and inflammatory markers. In colchicine-responsive patients, a mild negative correlation trend – though not statistically significant – was observed between IL-33 levels and inflammatory markers CRP and ESR (r values: -0.12 and -0.28; p values: 0.53 and 0.14), (Supplement 1).

DISCUSSION

In this study, we investigated the relationship between serum IL-33 levels and clinical and inflammatory parameters in patients with FMF. We found that serum IL-33 levels were higher in colchicine-responsive FMF patients than in healthy controls; however, no significant differences were observed between the colchicine-resistant group and healthy controls, nor between the colchicine-resistant and colchicine-responsive groups.

The role of IL-33 in various rheumatologic diseases has been well documented in the literature.

Earlier research has shown that IL-33 contributes to the pathogenesis of several rheumatic diseases, including rheumatoid arthritis, systemic lupus erythematosus and ankylosing spondylitis [17–21]. There is a paucity of studies examining IL-33 involvement in FMF. A recent study found that the carrier frequency of IL1RL1 deletion was significantly higher in FMF patients compared to healthy controls, suggesting that the IL-33–ST2 signaling pathway may be involved in the pathogenesis of FMF [10].

In our study, no statistically significant difference in serum IL-33 levels was observed between the overall patient cohort and the control group. In addition, no correlation was identified between IL-33 levels and clinical parameters or inflammatory markers. A previous study reported that IL-33 was not identified as a discriminative marker in FMF, consistent with our results [11]. In contrast, when serum IL-33 levels were evaluated across subgroups in our study, colchicine-responsive patients had higher levels than healthy controls. This finding suggests that, rather than reflecting a simple “patient–control” distinction, IL-33 may show a phenotype-related distribution in FMF.

Previous studies have shown that IL-33 does not require caspase-1-mediated processing to become biologically active; rather, caspase-1-cleaved IL-33 may be converted into inactive fragments [22]. This suggests that differences in the inflammasome/caspase-1 axis in FMF may influence serum IL-33 levels. On the other hand, the IL-33/ST2 axis has been described in the literature as a bidirectional “alarmin” pathway. Under certain conditions, it may enhance proinflammatory responses, whereas under others it has been reported to support T helper 2 (Th2)/T regulatory (Treg)-skewed regulatory responses and tissue homeostasis [6,23]. Within this framework, although higher IL-33 levels detected in colchicine-responsive patients during the attack-free period may suggest an immunoregulatory/compensatory response component, the cross-sectional design of our study does not allow a definitive determination of whether this finding reflects an epiphenomenon of the inflammatory microenvironment or a true regulatory mechanism. Longitudinal and mechanistic studies are needed to clarify this distinction.

The observation of higher serum IL-33 levels in colchicine-responsive patients may be related to the sensitivity of IL-33 biology to the inflammatory microenvironment and to the inflammasome/caspase-1 axis activity [22]. In the colchicine-resistant group, in whom ongoing inflammation and inflammasome/caspase activation may be more pronounced, a reduction in the biologically active form of IL-33 and relatively lower circulating levels may be observed. In addition, potential intergroup differences in the levels of regulatory components of the IL-33/ST2 axis, such as soluble ST2 (sST2), which binds IL-33, may influence IL-33 levels; however, since sST2 was not measured, this possibility could not be directly evaluated in our study [23].

A recent study including FMF patients has demonstrated that IL-33 levels were significantly higher during attack periods compared to non-attack periods and markedly increased during active inflammation [12]. In our study, IL-33 measurements were performed only during the attack-free period. The primary rationale for this approach was to evaluate whether serum IL-33 levels exhibit a discriminatory distribution among clinical phenotypes during the attack-free phase and to examine the potential pathophysiological role of IL-33 in a more stable clinical setting. Another reason for not sampling during attack periods was the practical difficulty of obtaining comparable attack-phase samples, given heterogeneity in attack frequency and timing across groups. The absence of both attack and attack-free measurements limits the

assessment of dynamic changes in IL-33 across disease phases and its potential phase-specific roles. Although attack and non-attack measurements were not assessed together in our study, when our findings are interpreted alongside the existing literature, they suggest that IL-33 may have a proinflammatory role during attacks, whereas it may exert more immunomodulatory effects during the attack-free period.

The importance of our study is reflected in the interpretation of IL-33 in FMF patients based on clinical phenotypes. The finding of higher IL-33 levels in colchicine-responsive patients compared with controls, demonstrated during the attack-free period, suggests that IL-33 may represent a signal associated with clinical phenotypes independently of conventional inflammatory markers. Because this finding was not observed across other subgroups, it should not be interpreted as evidence that IL-33 is a marker that “definitively predicts” colchicine response; rather, it should be considered as an observation that may contribute to the characterization of colchicine-response phenotypes.

Overall, our findings position IL-33 as a component of broader cytokine networks rather than an independent biomarker of activity in FMF.

LIMITATIONS

Our study has several limitations. Due to the cross-sectional design and single-time-point measurements, causal inferences regarding the relationships between IL-33 levels and clinical phenotypes cannot be made, nor can temporal dynamics be assessed. The single-center cohort and limited sample size may have reduced the power of subgroup analyses and restricted generalizability. Measuring IL-33 only during the attack-free period precluded comparisons between attack and non-attack periods and limited the evaluation of phase-specific dynamics. In addition, the lack of functional or mechanistic assessments of the IL-33/ST2 axis prevents direct testing of the biological basis of the observed associations. Therefore, larger, multicenter, longitudinal studies incorporating mechanistic components are needed to validate our findings.

CONCLUSION

In conclusion, in our study, serum IL-33 levels did not show a consistent association with FMF disease activity or classical inflammatory

markers; therefore, IL-33 does not appear to be a reliable activity biomarker. Nevertheless, the differences observed across clinical phenotypes suggest that IL-33 may have a potential role within

broader cytokine networks and immunoregulatory pathways in FMF. In this respect, the IL-33/ST2 axis should be evaluated alongside other cytokines in comprehensive, advanced immunological studies.

Introducere: Acest studiu a fost conceput pentru a evalua relația dintre nivelurile serice ale interleukinei-33 (IL-33) și caracteristicile clinice ale bolii la pacienții cu febră mediteraneană familială (FMF).

Metode: Populația studiată a inclus 54 de pacienți diagnosticați cu FMF (28 cu răspuns la colchicină și 26 rezistenți la colchicină) și 29 de subiecți sănătoși. Au fost comparate datele demografice, clinice, biochimice și markerii inflamatori, precum și nivelurile serice de IL-33.

Rezultate: Vârsta medie a pacienților cu FMF a fost de $34,3 \pm 9,8$ ani, iar 54% au fost de sex feminin. Pacienții rezistenți la colchicină au prezentat valori mediane ale proteinei C reactive semnificativ mai mari comparativ cu pacienții responsivi la colchicină și cu lotul martor (mediana [IQR]: 16 [30,4] mg/L, 2,9 [3,4] mg/L, respectiv 3,4 [2,8] mg/L; $p < 0,001$). Nivelurile mediane ale IL-33 serice au fost mai crescute la pacienții cu FMF comparativ cu martorii (273 [387] ng/L vs. 221 [179] ng/L, $p = 0,06$). Grupul responsiv la colchicină a prezentat valori ale IL-33 semnificativ mai mari față de lotul martor (287 [495] ng/L vs. 221 [179] ng/L, $p = 0,006$), în timp ce nu s-au observat diferențe semnificative între grupul rezistent la colchicină și martori (257 [219] ng/L vs. 221 [179] ng/L, $p = 0,74$). Nu au fost identificate corelații semnificative între nivelurile de IL-33 și markerii inflamatori sau caracteristicile clinice.

Concluzii: Nivelurile serice de IL-33 nu par a fi asociate cu activitatea bolii în FMF; totuși, creșterea observată la pacienții responsivi la colchicină ar putea sugera un rol imunomodulator sau compensator. Sunt necesare studii suplimentare, de amploare mai mare, pentru a clarifica rolul IL-33 în patogeneza FMF.

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Supplement 1

Relationship between clinical features, laboratory findings and IL-33

	All FMF Patients	Colchicine Responsive FMF	Colchicine Resistant FMF
Leukocyte count	p=0.77 r=0.03	p=0.49 r=-0.13	p=0.82 r=0.04
Neutrophil count	p=0.46 r=0.08	p=0.26 r=-0.21	p=0.26 r=0.22
Lymphocyte count	p=0.35 r=-0.10	p=0.93 r=0.01	p=0.03 r=-0.42
Hemoglobin	p=0.84 r=-0.02	p=0.53 r=0.12	p=0.77 r=-0.06
Thrombocyte	p=0.87 r=0.01	p=0.88 r=0.02	p=0.05 r=-0.37
Albumin	p=0.28 r=0.12	p=0.82 r=0.04	p=0.85 r=0.03
CRP	p=0.10 r=-0.17	p=0.53 r=-0.12	p=0.45 r=0.15
ESR	p=0.05 r=-0.21	p=0.14 r=-0.28	p=0.11 r=-0.31

Note: CRP: C reactive protein, ESR: erythrocyte sedimentation rate