CMJ. 2024;46(1):57-65
DOI: 10.7197/cmj.1431762

Cumhuriyet Medical Journal

| cmj.cumhuriyet.edu.tr | Founded: 2004 Available online, ISSN:1305-0028 Publisher: Sivas Cumhuriyet Üniversitesi

Determination of Serum Interleukin-36 Alpha, Beta, Gamma and Interleukin-17 Levels in Patients with Multiple Myeloma

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Research Article

History

Received: 06/02/2024
Accepted: 23/03/2024

ABSTRACT

Objective: Multiple myeloma (MM) is a hematologic malignancy characterized by bone marrow infiltration of clonal plasma cells. Today, there is no treatment for obtaining a complete cycle for MM. IL-36 is a cytokine composed of three agonists named alpha, beta, and gamma. Its increase in inflammation has been proven in the literature. It is also reported that IL-17 plays a role in some rheumatologic and malignant diseases together with inflammation.

Methods: The aim of the study is to figure out the roles, if any, of IL-36 and IL-17 in the pathogenesis of MM depending on their known physiology and to contribute to the literature to find new treatment options.

33 newly diagnosed MM patients who had never received any treatment and 33 healthy volunteers were included in the study. Basic laboratory parameters and interleukin levels in myeloma patient group and healthy group were included in the study.

Results: In the study, it was found that IL-36 alpha, beta, gamma, and IL-17 levels were statistically significantly lower in the disease group when compared to the healthy group. A negative correlation was found between IL-17 measurement and beta-2 microglobulin. Therefore, it was thought that IL-17 may be a marker to predict prognosis.

Conclusion: In conclusion, we think that IL-36 and IL-17 may play a role in the etiopathogenesis of MM and IL-36 alpha and IL-17 may be associated with prognosis. However, there is a need for more comprehensive studies.

Keywords: Multiple myeloma, Interleukin 36, Interleukin 17

Multipl Myelomali Hastalarda Serum İnterlökin-36 Alfa, Beta, Gama; İnterlökin-17 Düzeyinin Belirlenmesi

Araştırma Makalesi

Süreç

Geliş: 06/02/2024
Kabul: 23/03/2024

ÖZET

Amaç: Multipl myelom (MM), klonal plazma hücrelerinin kemik iliği infiltrasyonu ile karakterize hematolojik bir malignitedir. Günümüzde halen MM için tam kür elde edecek tedavi yoktur. IL-36; alfa, beta ve gama isimli üç agonistten oluşan bir sitokindir. İnflamasyondaki artışı literatürde kanıtlanmıştır. IL-17'nin ise inflamasyonla birlikte bazı romatolojik ve malign hastalıklarda rol oynadığı literatürde bildirilmiştir.

Yöntem: Bizim amacımız IL-36 ve IL-17'nin bilinmekte olan fizyolojilerinden yola çıkarak MM patogenezindeki rollerini anlayabilmek, yeni tedavi seçenekleri bulunabilmesi için literatüre katkı sağlamaktır.

Çalışmamıza 33 yeni tanı hiç tedavi almamış MM hastası ve 33 sağlıklı gönüllü alındı. Myelom hasta grubu ve sağlıklı grupta temel laboratuvar parametreleri, interlökin düzeyleri çalışmaya dahil edildi.

Bulgular: Çalışmamızda IL-36 alfa, beta, gama ve IL-17 düzeyi sağlıklı gruba göre hastalıklı grupta istatiksel olarak anlamlı şekilde düşük saptandı. IL-17 ölçümü ile beta-2 mikroglobulin arasında negatif yönlü bir ilişki bulduk. Bu nedenle IL-17 nin prognozu öngörmede bir belirteç olabileceğini düşündük.

Sonuç: Sonuç olarak, IL-36 ve IL-17'nin MM etiyopatogenezinde rolü olabileceğini, IL-36 alfa ve IL-17'nin prognoz ile ilişkili olabileceğini düşünüyoruz. Ancak daha geniş kapsamlı çalışmalara ihtiyaç vardır.

Anahtar Kelimeler: Multipl myelom, Interlökin 36, Interlökin 17

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How to Cite: Yıldız Bilge N, Terzi H, Doğan HO, Kablan D, Şencan M. Determination of Serum Interleukın-36 Alpha, Beta, Gamma and Interleukın-17 Levels in Patients with Multiple Myeloma. Cumhuriyet Medical Journal. 2024;46(1):57-65

Introduction

Multiple myeloma is a malignant neoplasm of plasma cells, that is characterized by the proliferation of bone marrow plasma cells and begins with an asymptomatic premalignant MGUS stage. It accounts for approximately 10% of hematologic malignant diseases.[1] The bone marrow stromal cell is a mononuclear, fibroblast-like cell that supports hematopoietic development. Adherence of MM cells activates the bone marrow stromal cells. Activation of the NF-kB pathway in stromal cells causes the secretion of proliferative, anti-apoptotic and chemotactic cytokines such as interleukin-6, stromal cell-derived factor-1 and insulin-like growth factor-1 and all of them directly support the continued adherence, growth and proliferation of MM cells.[2]

Interleukin-36 (IL-36) is a member of the IL-1 family and it is included three agonists (IL-36 alpha, beta, gamma), an antagonist (IL-Ra), a receptor (IL-36R) and an accessory protein (IL-36RAcP).[3] IL-36 is expressed in monocytes, T/B lymphocytes, spleen, bone marrow, tonsil, skin and lymph nodes.[4] In vitro and in vivo studies have shown that IL-36 and its receptor-mediated signaling mechanisms are involved in the processes governing fibrosis leading to organ failure or dysfunction. IL-36R is highly synthesized in the epithelial and skin cells and in the esophagus, thyroid, kidney, adrenal gland, and gallbladder.[5] However, it is observed that IL-36 mRNA is synthesized at the highest rate in keratinocytes.[6] IL-36 beta can stimulate its own synthesis and thanks to this feature, it is similar to the autocrine/paracrine cycle of IL-1. IL-17 and TNF are the molecules stimulating the synthesis of IL-36 alpha, IL-36 beta, and IL-36 gamma in keratinocytes. Various studies have also revealed that epidermal growth factor plays a role in the synthesis of IL-36 alpha and IL-36 beta in the skin. IL-36 gamma increase is triggered in the bronchial epithelium, which is exposed to intense inflammatory stimuli. High rates of IL-36 alpha and gamma are synthesized in the infected skin of the patients with psoriasis and in the lesioned skin of the patients with atopic dermatitis.[7]

IL-17 is a proinflammatory cytokine involved in the pathogenesis of autoimmune and inflammatory diseases together with various bacterial, fungal and viral infections.[8] IL-17 family has 6 forms (IL-17 A-F).[9] The interleukin-17 receptor (IL-17R) family consists of five members (IL-17R A to IL-17RE).[10] Recently, it is reported that IL-17C binds to IL-17RE and activates NF-kB.[11] The main targets of IL-17 are mesenchymal and myeloid cells.[12] IL-17 plays a role in the pathogenesis of diseases such as rheumatoid arthritis, systemic lupus erythematosus (SLE), inflammatory bowel diseases and psoriasis.[13] In addition, it takes also part in the pathogenesis of solid organ tumors such as cervix, esophagus, stomach, colorectal and hepatocellular cancer.[14]

The aim of the current study is to understand the possible roles of IL-36 and IL-17 in the pathogenesis of multiple myeloma and to contribute to the literature for new treatment options.

Materials and Methods

The present study was conducted with the approval of Sivas Cumhuriyet University Interventional Clinical Trials Ethics Committee (Decision No: 2022-02/01). The study was funded by Sivas Cumhuriyet University Scientific Research Projects (CÜBAP) with project number T-2022-973. In the study, 33 patients with MM, who accepted to Sivas Cumhuriyet University Faculty of Medicine Hematology Clinic, were newly diagnosed and had been never treated were included. The control group consisted of 33 volunteers, who were over 18 years of age, had no comorbidities and no regular medications, were not pregnant, were not smokers, had no active infection, had no diagnosed active malignancy, and no history of malignancy.

In the present study, the blood tests at the time of admission were used as routine blood tests. In the patient group, blood samples were taken at the time of diagnosis without receiving treatment. No blood samples were taken again during other stages of treatment. ISS (International Staging System) was used to determine the disease stages. The presence of bone fractures at the time of diagnosis was decided based on positron emission computed tomography (PET/CT), computed tomography and if any, magnetic resonance imaging reports.

During the study period, blood was collected from the peripheral vein of newly diagnosed MM patients and of the healthy control group into suitable tubes after at least eight hours of fasting for IL-36 alpha, IL-36 beta, IL-36 gamma, IL-17 levels and laboratory measurements. Serum IL-6 levels were also studied in the patient group from blood samples at the time of diagnosis. The blood samples were centrifuged at 2300g 4000 rpm for 10 minutes and stored in an Eppendorf tube at -80ºC. SunRed branded enzyme-linked immunosorbent assay (ELISA) kit was used for IL-36 alpha, IL-36 beta, IL-36 gamma, and IL-17 measurements.

Statistics

Data were analyzed with SPSS 27.0 program at confidence level of 95%. Mean, standard deviation (Mean±SD), minimum, maximum, median (M) statistics were given for the measurements. In the study, Mann Whitney/independent samples t-test was used the comparison of two groups, Kruskal Wallis/one-way ANOVA test for more than two groups, Chi-square test for the correlation between the grouped variables, and Pearson/Spearman correlation test for the correlation between numerical measurements. According to the results of normal distribution, t-test, ANOVA, and Pearson correlation tests were used for the normally distributed measurements and Mann Whitney U test was used for non-normally distributed measurements.

Results

Baseline Data

In the study, 33 MM patients and 33 healthy volunteers, who evaluated to Sivas Cumhuriyet University Faculty of Medicine Hematology Clinic, were included. In the MM patient group, 39.4% (n=13) were younger than 65 years of age and 60.6% (n=20) were over the age of 65. In the healthy

group, 66.7% (n=22) were under the age of 65 and 33.3% (n=11) were over the age of 65. In the MM patient group, 39.3% (n=13) were female and 60.6% (n=20) were male; while in the healthy group, 60.6% (n=20) were female and 39.4% (n=13) were male.

In the MM patient group, 30.3% (n=10) had IgG kappa type, 24.2% (n=8) had IgG lambda type, 6.1% (n=2) had IgA kappa type, 18.2% (n=6) had IgA lambda type, 12.1% (n=4) had kappa light chain myeloma, 6.1% (n=2) had lambda light chain myeloma, and 3% (n=1) had non-secretory type myeloma (Table 1).

Table 1. The Correlation of Clinical Characteristics with Gender in MM Patient Group

n(%)		Female	Male	Total	p
MM type	IgG kappa	7 (53.8)	3 (15)	10 (30.3)	
	IgG lambda	3 (23.1)	5 (25)	8 (24.2)	
	IgA kappa	0 (0)	2 (10)	2 (6.1)	
	IgA lambda	0 (0)	6 (30)	6 (18.2)	0.023*
	Kappa light chain myeloma	1 (7.7)	3 (15)	4 (12.1)	
	Lambda light chain myeloma	2 (15.4)	0 (0)	2 (6.1)	
	Non-secretory type myeloma	0 (0)	1 (5)	1 (3)	
Stage at the time of diagnosis (According to ISS)	Stage 1	3 (23.1)	3 (15)	6 (18.2)	
	Stage 2	3 (23.1)	6 (30)	9 (27.3)	0.799
	Stage 3	7 (53.8)	11 (55)	18 (54.5)	
Monoclonal gammopathy in blood immunofixation	Non-available	2 (16.7)	1 (5)	3 (9.4)	0.540
	Available	10 (83.3)	19 (95)	29 (90.6)	
Monoclonal gammopathy in urine immunoelectrophoresis	Non-available	0 (0)	5 (38.5)	5 (29.4)	0.261
	Available	4 (100)	8 (61.5)	12 (70.6)	
Bone involvement in PET at diagnosis	Non-available	1 (7.7)	5 (26.3)	6 (18.8)	0.361
	Available	12 (92.3)	14 (73.7)	26 (81.3)	
Fracture at diagnosis	Non-available	10 (76.9)	16 (84.2)	26 (81.3)	0.666
	Available	3 (23.1)	3 (15.8)	6 (18.8)	

At diagnosis, 54.5% (n=18) of the patients were in stage 3, 27.3% (n=9) patients in stage 2, and 18.2% (n=6) patients in stage 1. At the time of diagnosis, 81.3% (n=26) of the patients had bone involvement on PET/CT, and also 18.8% (n=6) patients had fractures (Table 1). A statistically significant correlation was found between gender and MM type groups in the MM patient group (p=0.023 <0.05). While the incidence of IgG kappa was higher in females (53.8%), the incidence of IgA lambda was higher in males (30.0%). The relationship of other clinical characteristics with gender was not significant (p>0.05) (Table 1).

Table 2 shows the treatments and treatment responses of the patients in the multiple myeloma group.

Comparison of Interleukin 36 alpha, Interleukin 36 beta, Interleukin 36 gamma and Interleukin 17 Levels with Other Parameters

There was a statistically remarkable difference between MM patient group and healthy group in terms of IL-36 alpha (p<0.001), IL-36 beta (p<0.001), IL-36 gamma (p<0.001), and IL-17 (p<0.001) measurements. IL-36 alpha (28.6 ng/L), IL-36 beta (17.89 ng/L), IL-36 gamma (22.63 ng/L), IL-17 (398.32 pg/ml) measurements were higher in the healthy group when compared to the MM patient group (Table 3).

There was a statistically remarkable difference between genders in the MM patient group in terms of IL-36 alpha (p=0.033 <0.05) measurements. IL-36 alpha (13.14 ng/L) was higher in men. The difference in other measurements was not statistically significant (p>0.05).

In the MM patient group, there was no statistically remarkable difference between those who responded to first- and second-line treatment and those who did not in terms of IL measurements (p>0.05). In this group, IL-36 beta measurements were higher in those who did not respond to third-line treatment and this difference was statistically significant **(p=0.029 <0.05)**. The difference was not remarkable for other IL measurements (p>0.05) (Table 4).

There was a negative, statistically remarkable correlation between IL-36 alpha measurement and albumin (r=-0.404, p=0.020<0.05) measurement in MM patient group. There was a negative, statistically remarkable correlation between IL-36 beta measurement and albumin (r=-0.410, p=0.018<0.05) measurement. Also, a negative, statistically remarkable correlation was found between IL-36 gamma measurement and platelet count (r=-0.400, p=0.021<0.05). There was a negative and statistically remarkable correlation between IL-17 measurement and beta2 microglobulin (r=0.389, p=0.025<0.05) measurement. The correlations between other measurements were not remarkable (p>0.05). There was a positive statistically remarkable correlation between IL-6 measurement and BUN (r=0.535, p<0.05) and a negative statistically remarkable correlation with albumin (r=-0.441, p<0.05) and lymphocyte count (r=-0.406, p<0.05).

Table 2. Treatment Characteristics in MM Patient Group

n (%)		Stage 1	Stage 2	Stage 3
First-line treatment	Drug-free follow up	2 (33.3)	0 (0)	0 (0)
	VCD	3 (50)	7 (87.5)	14 (77.8)
	Vel-dex	0 (0)	0 (0)	2 (11.1)
	MP	0 (0)	0 (0)	1 (5.6)
	AVD	1 (16.7)	1 (12.5)	1 (5.6)
First-line treatment response	Non-available	3 (100)	3 (37.5)	6 (42.9)
	Available	0 (0)	5 (625)	8 (57.1)
Receiving RT	Did not receive	4 (80)	8 (100)	10 (71.4)
	Received	1 (20)	0 (0)	4 (28.6)
ASCT	Not done	5 (100)	4 (50)	9 (64.3)
	Done	0 (0)	4 (50)	5 (35.7)
Second-line treatment	VCD	4 (80)	1 (20)	1 (8.3)
	Vel-dex	0 (0)	0 (0)	2 (16.7)
	Len-dex	1 (20)	2 (40)	6 (50)
	Lenalidomide	0 (0)	1 (20)	3 (25)
	VRD	0 (0)	1 (20)	0 (0)
Second-line treatment response	Non-available	2 (40)	2 (50)	6 (66.7)
	Available	3 (60)	2 (50)	3 (33.3)
ASCT after second-line treatment	Not done	1 (20)	2 (100)	8 (100)
	Done	4 (80)	0 (0)	0 (0)
Third-line treatment	MP	0 (0)	0 (0)	1 (16.7)
	Len-dex	2 (50)	0 (0)	1 (16.7)
	Len-dex+ixazomib	1 (25)	0 (0)	2 (33.3)
	CRD	0 (0)	1 (50)	0 (0)
	Daratumab	0 (0)	0 (0)	0 (0)
	Lenalidomide	1 (25)	1 (50)	0 (0)
	Vel-dex	0 (0)	0 (0)	1 (16.7)
	Pom-Dex	0 (0)	0 (0)	1 (16.7)
Third-line treatment response	Non-available	1 (25)	1 (100)	2 (66.7)
	Available	3 (75)	0 (0)	1 (33.3)
ASCT after third-line treatment	Not done	3 (75)	1 (100)	2 (66.7)
	Done	1 (25)	0 (0)	1 (33.3)

*p<0.05 means there is a significant correlation, p>0.05 means there is no significant correlation; Chi-square test (% according to both stage and MM type)
ASCT:Autologous stem cell transplantation, VCD:Bortezomib+Cyclophosphamide+Dexamethasone), Vel-dex:Bortezomib+ dexamethasone MP:Melphalan+prednisolone, AVD: Adriamisin+ Vincristine+Dexamethasone, len-dex:Lenalidomide+dexamethasone,VRD:Bortezomib+ Lenalidomide +Dexamethasone, CRD: Lenalidomide+bortezomib+Dexamethasone, Pom-Dex: Pomalidomid+Dexamethasone

Table 3. Comparison of Interleukin Clinical Measurements According to the Patient Groups

	Patient	Control	Test/p
Interleukin 36 alpha (ng/L)	11.55 (10.25-13.96)	23.44 (12.57-41.31)	U=195.0/ 0.000*
Interleukin 36 beta (ng/L)	4.22 (2.86-5.24)	14.57 (5.42-27.33)	U=180.0/ 0.000*
Interleukin 36 gamma (ng/L)	6.08 (4.88-6.93)	12.97 (7.31-36.77)	U=167.5/ 0.000*
Interleukin 17 (pg/ml)	94.82 (67.11-117.45)	298.29 (135.56-607.67)	U=105.0/ 0.000*

*p<0.05 means there is a significant correlation, Mann Whitney U test

Overall Survival Measurements

Overall survival: Minimum 1 month, maximum 23 months. In the patient group, 14 patients died and 19 patients are still being followed. There was a statistically remarkable difference between deceased and living patients in the MM patient group in IL-36 alpha and IL-6 measurements (p<0.05). IL-36 alpha and IL-6 measurements were higher in deceased patients. The difference was not remarkable for other IL measurements (p>0.05) (Table 5).

Table 4. Comparison of Interleukin Measurements in the MM Patient Group According to Response to Treatment Status

	First-line treatment		Test/p
	No Response	Response	
Interleukin 36 alpha (ng/L)	13.2 (10.25-15.24)	10.85 (9.61-14.26)	U=64.5/ 0.470
Interleukin 36 beta (ng/L)	4.08 (3.39-5.96)	3.9 (2.39-5.16)	U=68.0/ 0.611
Interleukin 36 gamma (ng/L)	6.65 (5.1-8.77)	6.46 (4.95-6.93)	U=63.0/ 0.437
Interleukin 6 (pg/ml)	9.94 (4.6-16.22)	11.9 (6.31-19.3)	U=65.0/ 0.503
Interleukin 17 (pg/ml)	96.39±32.71	94.68±26.59	t=0.144/ 0.886
	Second-line treatment		Test/p
	No Response	Response	
Interleukin 36 alpha (ng/L)	11.58 (10.14-14.89)	12.8 (11.5-15.6)	U=26.0/ 0.237
Interleukin 36 beta (ng/L)	3.69 (3.63-5.48)	4.3 (1.79-4.89)	U=36.0/ 0.611762
Interleukin 36 gamma (ng/L)	6.54 (5.88-7.77)	6.78 (4.89-7.07)	U=38.0/ 0.897
Interleukin 6 (pg/ml)	7.66 (3.9-15.46)	17.9 (4.57-21.95)	U=28.5/ 0.315
Interleukin 17 (pg/ml)	93.21±25.95	102.49±25.27	t=-0.762/ 0.457
	Third-line treatment		Test/p
	No Response	Response	
Interleukin 36 alpha (ng/L)	12.24 (9.94-15.60)	12.25 (10.62-14.78)	U=8.0/ 0.999
Interleukin 36 beta (ng/L)	4.34 (3.99-5.03)	3.76 (3.70-3.86)	U=0.0/ 0.029*
Interleukin 36 gamma (ng/L)	6.70 (4.79-8.54)	5.69 (4.83-9.18)	U=8.0/ 0.999
Interleukin 6 (pg/ml)	16.60 (7.33-23.35)	2.83 (1.89-5.03)	U=1.0/ 0.057
Interleukin 17 (pg/ml)	104.71±16.83	111.19±31.35	t=-0.364/ 0.728

*p<0.05 means there is a significant correlation, t/Mann Whitney U test

Discussion

Multiple Myeloma (MM) is a disease characterized by the accumulation of malignant clonal plasma cells in the bone marrow. It accounts for 1% of all cancers and 10% of hematologic cancers. The mean age at the time of diagnosis of myeloma reported in the literature is 69 years. During diagnosis, less than 3% of the patients are under the age of 40 years and 38% are 70 years and older .[1,15] In the present study, the mean age at the time of diagnosis was found to be 68.73±9.69 years, which is compatible with the literature. In addition, 39.4% (n=13) of the patients were under 65 years and 60.6% (n=20) were over 65 years .[16] However, in the present study, the mean age of the healthy group was remarkable lower than the mean age of the patient group. Due to the increase in comorbidities and susceptibility to infection with advancing age, it was difficult to find a healthy group at the old age group who met the inclusion criteria of being voluntary for the study, being over the age of 18, having no comorbidities or no regular medications, being non-pregnant, being non-smoker, having no active infection, having no diagnosed active malignancy, and having no history of malignancy. This is one of the limitations of the present study. In multiple myeloma, low albumin level is associated with poor prognosis. Since albumin induces cell growth stabilization and DNA replication with its antioxidant property, low albumin level affects prognosis negatively. There are also studies reporting a negative correlation between serum IL-6 level and serum albumin level in patients with myeloma .[17] The present study reported a statistically significant negative correlation between IL-6 level and albumin level which is compatible with the literature.

In the present study, a statistically significant difference was found between the MM patient group and the healthy group in terms of IL-36 alpha, IL-36 beta, IL-36 gamma, and IL-17 measurements. The mean values of IL-36 alpha (28.6 ng/L), IL-36 beta (17.89 ng/L), IL-36 gamma (22.63 ng/L), and IL-17 (398.32 pg/ml) measurements were higher in the healthy group when compared to the MM patient group. When IL levels were compared in terms of gender, IL-36 alpha (13.14 ng/L) measurement was higher in males. Also, in the MM patient group, IL-36 beta (4.46 ng/L) was higher in the patients who did not respond to third-line treatment when compared to the patients who responded. Although there is no data in the literature in this respect, we think that there is a need for further studies.

IL-36 has an important role in the etiopathogenesis of autoimmune, inflammatory, and malignant diseases such as psoriasis, chronic lung diseases, inflammatory bowel disease, rheumatoid arthritis, allergic rhinitis, Sjögren's syndrome and SLE. IL-36R is mostly expressed in the skin, gastrointestinal system, ovaries, lung, kidney, and lymphoid organs .[18-21] In the literature, studies aiming at understanding the action and synthesis mechanism of IL-36 have been mostly conducted in the field of dermatology and there are a limited number of studies on solid organ cancers and hematologic malignancies.

Johnston et al., demonstrated the role of IL-36 in pustular skin diseases in their study conducted in patients with pustular psoriasis.[22] There are literature information reporting that anakinra, an IL-1 receptor antagonist, and spesolimab, an IL-36 receptor blocker, are used in the treatment of generalized pustular psoriasis .[23,24]

Table 5. Comparison of Interleukin Measurements in MM Patient Group According to Living Status

	Living Status		Test/p
	Deceased	Living	
IL 36 alpha (ng/L)	13.49 (11.46-15.48)	10.26(9.79-12.74)	U=67.0/ 0.013*
IL 36 beta (ng/L)	5.05 (3.78-5.29)	3.72 (2.41-4.62)	U=89.0/ 0.100
IL 36 gamma (ng/L)	6.08 (5.14-8.01)	6.12 (4.81-6.74)	U=108.0/ 0.343
IL 6 (pg/ml)	17.40 (10.8-22.3)	9.26 (3.75-13.82)	U=71.5/ 0.020*
IL 17 (pg/ml)	101.76±35.16	91.44±26.13	t=0.967/ 0.341

*p<0.05 means there is a significant correlation, t/Mann Whitney U test, IL Interleukin

In their study, Al-Awaisi et al., demonstrated that IL-36 alpha, IL-36 beta and IL-36R expression increased with age in mouse heart. They reported that the damage caused by ischemia reperfusion decreased, blood flow improved, and neutrophil migration decreased with IL-36R antagonist administration and suggested that the agents targeting IL-36/IL36R pathway may be used in the treatment of ischemia reperfusion in older patients.[25]

When the solid organ cancers are examined, in their study conducted on the pathologic tissue cell culture of 20 patients with lung carcinoma, Backer et al., indicated that there was a significant increase in IL-36α, IL-36γ and IL-36R protein expression. They also revealed that stimulation of cancer cells with IL-36γ may increase the expression of the immune checkpoint protein PD-L1 (Programmed Death-Ligand 1).[26]

In the study conducted by Pan et al. with hepatocellular carcinoma cell culture; associated decreased intra-tumoral IL-36 alpha expression with poor prognosis and considered that IL-36 alpha may mediate anti-tumor immune responses by including CD3 and CD8 T lymphocytes in the tumor site and activating adaptive immunity.[27]

In their study, Chen et al., included the tumoral tissues of 185 patients with colorectal cancer, who had not received neoadjuvant chemotherapy, and 130 non-tumoral normal tissues and demonstrated that colonic IL-36 alpha, IL-36 beta, and IL-36 gamma significantly decreased in the patient group when compared to the matched non-colorectal carcinoma tissues. In the same study, patients with high IL-36 alpha level had a better survival. In IL-36 gamma, an opposite situation was found and patients with low IL-36 gamma levels had higher survival rates.[28] In their previous study, Pan et al., thought that IL-36 alpha showed anti-tumor effect by activating adaptive T-cell immune responses in colorectal carcinoma.[27] A negative correlation between IL-36 alpha measurement and albumin level (r=-0.404, p=0.020 <0.05) in the MM patient group and the higher IL-36 alpha measurement (13.76 ng/L) in deceased patients when compared to living patients in the myeloma patient group in the present study suggest that IL-36 alpha may be associated with prognosis. However, no significant correlation was found between overall survival and IL levels. It is considered that this may be caused by the insufficient number of patients and further clinical studies are needed.

In their study, Wang et al., found that IL-36 gamma supported directly the effector exchange of type 1 lymphocytes in vitro and showed a strong anti-tumor immune response in vivo.[29] In their study, Chen et al., revealed the anti-tumorigenic role of IL-36 gamma in a breast cancer cell line. Via the application of IL-36 gamma-expressing plasmid and doxorubicin together to breast carcinoma cell lines, it was shown that IL-36γ and doxorubicin-loaded micelles remarkable reduced the metastasis.[30]

In contrast to these data, Le et al., reported that IL-36 gamma showed pro-tumorigenic effect by stimulating extracellular signal-regulated kinase (ERK) 1/45 activation in their study on gastric cancer.[31]

In the literature, it has been reported that IL-36 cytokine family shows both pro-tumorigenic and anti-tumorigenic activity in various cancer types. It is thought that more extensive molecular studies are required to resolve this dilemma and to further clarify the etiopathogenesis.

It is known that leukemic progenitor cells infiltrating the bone marrow in acute myeloid leukemia express more IL-36 than normal hematopoietic progenitor cells.[32]

In their in-vivo mouse epidermis and in-vitro primary human keratinocyte culture studies, Carrier et al., demonstrated that IL-36s were not only regulated by Th17 cytokines but they can also regulate the expression of Th17 cytokines themselves .[33]Under the light of this information, IL-17 blockers have taken their place in the treatment of dermatologic diseases. Also, even secukinumab, which is an IL-17A monoclonal antibody, was approved for the treatment of moderate/severe psoriasis in 2015. [34]

In their study, Chiricozzi et al., reported that IL-17/TNF-α interactions were present not only in epidermal keratinocytes but also in some leukocytes. [35] The relationship between chronic inflammation and cancer has been previously reported in the literature. It is suggested that approximately 15% of all human cancers are caused by infection and chronic inflammation.[36] IL-17 is a proinflammatory cytokine proven to be effective in the development of prostate, colon, skin, breast, lung and pancreatic cancers .[37-42] In their study, Zhang et al., showed that IL-17 played a role in the pathogenesis of prostate cancer. In line with these results, they stated that IL-17 is a potential target for developing new strategies in the prevention and treatment of prostate cancer.[43]

In the literature, there are reports stating that IL-17 has both pro-tumorigenic and anti-tumorigenic roles [44]. In their study, Kryczek et al., reported that IL-17 ectopically expressed in tumor cells suppressed tumor progression through increased anti-tumor immunity in immune-competent mice and stimulated tumor progression through increased inflammatory angiogenesis in immune-suppressive mice.[45]

Novitskiy et al., conducted a study on breast carcinoma cells and revealed that IL-17, secreted by Th17 cells, caused a tumor-progressing effect by increasing the pro-tumorigenic characteristics of myeloid cells.[40]

On the contrary, Chen et al., conducted a study on 192 patients with gastric adenocarcinoma and found that the patients with high IL-17 levels had remarkably higher five-year survival rate than those with low levels .[46] Benchetrit et al., carried out a study by transplanting hematopoietic tumors (plasmacytoma and mastocytoma) into immunocompetent mice and reported that IL-17 inhibited the tumor growth rate and the pro-tumor or anti-tumor effects of IL-17 on tumor development was associated with immunity.[47]

Bankır et al., compared the median levels of serum IL-17 and IL-23 in the patients with early-stage chronic lymphocytic leukemia (CLL) with the healthy control group and found no statistically significant difference. They reported that this may be caused by the result of the early stage of the patients.[48]

In the study conducted by Tang et al., on the patients with CLL; all of IL-6, IL-17 and IL-23 levels were found to be significantly higher in the serum samples of CLL patients; whereas, TGF-β1 and IL-10 concentrations were much lower than the controls. They suggested that this situation was due to the fact that the normal cytokine microenvironment was damaged in CLL. The median IL-17 level in the patients with CLL in that study was found to be 3.23 pg/mL, which is significantly lower than the levels in the present study.[49]

In their study, Alexandrakis et al., compared serum IL-17 levels of 40 myeloma patients who had never received any treatment with a healthy control group; however, they found no statistically significant difference. [50] In the present study, no statistically significant difference was found in IL-17 measurements between the stage groups in the MM patient group.

In their study, Lemancewicz et al., compared IL-17A and IL-17E levels in 34 patients with newly diagnosed myeloma with the healthy group and found that IL-17E levels were significantly higher in the myeloma group. As a result, they concluded that IL-17 may both stimulate and suppress tumor growth and there is a balance between the effects of IL-17A and IL-17E and they emphasized that more comprehensive studies are needed .[51]

Consequently, even though the role of IL-36 and IL-17 in dermatologic diseases is more clearly understood, it is thought that they may have a role in the etiopathogenesis of solid organ cancers and hematologic malignancies. When the literature data is examined, this issue has not yet been clarified. The use of IL-36 and IL-17 blocks in the treatment in dermatology arouses curiosity in terms of new options for myeloma treatment. In addition, it may be useful in predicting prognosis in myeloma depending on the studies conducted on solid organ cancers in the literature. Therefore, it is thought and recommended to conduct further comprehensive molecular studies in myeloma.

References

1. Firth J. Haematology: multiple myeloma. Clin Med (Lond). Ocak 2019;19(1):58-60.
2. Brigle K, Rogers B. Pathobiology and Diagnosis of Multiple Myeloma. Seminars in Oncology Nursing. 01 August 2017;33(3):225-36.
3. Zhou L, Todorovic V. Interleukin-36: Structure, Signaling and Function. Adv Exp Med Biol. 2021;21:191-210.
4. Gresnigt MS, van de Veerdonk FL. Biology of IL-36 cytokines and their role in disease. Semin Immunol. 15 Dec 2013;25(6):458-65.
5. Melton E, Qiu H. Interleukin-36 Cytokine/Receptor Signaling: A New Target for Tissue Fibrosis. Int J Mol Sci. 04 September 2020;21(18):6458.
6. Yazdi AS, Ghoreschi K. The Interleukin-1 Family. Adv Exp Med Biol. 2016;941:21-9.
7. Walsh PT, Fallon PG. The emergence of the IL-36 cytokine family as novel targets for inflammatory diseases. Ann N Y Acad Sci. April 2018;1417(1):23-34.
8. Yan JW, Wang YJ, Peng WJ, Tao JH, Wan YN, Li BZ, Mei B, Chen B, Yao H, Yang GJ, Li XP, Ye DQ, Wang J. Therapeutic potential of interleukin-17 in inflammation and autoimmune diseases. Expert Opin Ther Targets. January 2014;18(1):29-41.
9. Amatya N, Garg AV, Gaffen SL. IL-17 Signaling: The Yin and the Yang. Trends in Immunology. 01 May 2017;38(5):310-22
10. Ritzmann F, Lunding LP, Bals R, Wegmann M, Beisswenger C. IL-17 Cytokines and Chronic Lung Diseases. Cells. Ocak 2022;11(14):2132.
11. Iwakura Y, Ishigame H, Saijo S, Nakae S. Functional specialization of interleukin-17 family members. Immunity. 25 Fab 2011;34(2):149-62.
12. Xu S, Cao X. Interleukin-17 and its expanding biological functions. Cell Mol Immunol. Mayıs 2010;7(3):164-74.
13. Onishi RM, Gaffen SL. Interleukin-17 and its target genes: mechanisms of interleukin-17 function in disease. Immunology. 2010;129(3):311-21.
14. McGeachy MJ, Cua DJ, Gaffen SL. The IL-17 Family of Cytokines in Health and Disease. Immunity. 16 Nisan 2019;50(4):892-906.
15. Türk Hematoloji Derneği Multipl Myelom Tanisi Ve Tedavi Kilavuz. Galenos Yayınevi, Mart-2020.
16. Hussain A, Almenfi HF, Almehdewi AM, Hamza MS, Bhat MS, Vijayashankar NP. Laboratory Features of Newly Diagnosed Multiple Myeloma Patients. Cureus. 22 May 2019;11(5):e4716.
17. Cai Y, Zhao , Dai Q, Xu M, Xu X, Xia W. Prognostic value of the albumin-globulin ratio and albümin globulin score in patients with multiple myeloma. J Int Med Res. March 2021;49(3):300060521997736.
18. Dong H, Hao Y, Li W, Yang W, Gao P. IL-36 Cytokines: Their Roles in Asthma and Potential as a Therapeutic. Front Immunol. 2022;13:921275.
19. Scheibe K, Kersten C, Schmied A, Vieth M, Primbs T, Carlé B, Knieling F, Claussen J, Klimowicz AC, Zheng J, Baum P, Meyer S, Schürmann S, Friedrich O, Waldner MJ, Rath T, Wirtz S, Kollias G, Ekici AB, Atreya R, Raymond EL, Mbow ML, Neurath MF,

Neufert C. Inhibiting Interleukin 36 Receptor Signaling Reduces Fibrosis in Mice With Chronic Intestinal Inflammation. Gastroenterology. 01 March 2019;156(4):1082-1097.e11
20. Nishida A, Hidaka K, Kanda T, Imaeda H, Shioya M, Inatomi O, Bamba S, Kitoh K, Sugimoto M, Andoh A. Increased Expression of Interleukin-36, a Member of the Interleukin-1 Cytokine Family, in Inflammatory Bowel Disease. Inflammatory Bowel Diseases. 01 February 2016;22(2):303-14.
21. Chen W jian, Yu X, Yuan XR, Chen B jie, Cai N, Zeng S, Sun Y song, Li H wen. The Role of IL-36 in the Pathophysiological Processes of Autoimmune Diseases. Front Pharmacol. 2021 Oct 5;12:727956.
22. Johnston A, Xing X, Wolterink L, Barnes DH, Yin Z, Reingold L, Kahlenberg JM, Harms PW, Gudjonsson JE. IL-1 and IL-36 are dominant cytokines in generalized pustular psoriasis. Journal of Allergy and Clinical Immunology. 01 Temmuz 2017;140(1):109-20.
23. Hüffmeier U, Wätzold M, Mohr J, Schön MP, Mössner R. Successful therapy with anakinra in a patient with generalized pustular psoriasis carrying IL36RN mutations. British Journal of Dermatology. 01 Ocak 2014;170(1):202-4.
24. Burden AD. Spesolimab, an interleukin-36 receptor monoclonal antibody, for the treatment of generalized pustular psoriasis. Expert Review of Clinical Immunology. 04 Mayıs 2023;19(5):473-81.
25. El-Awaisi J, Kavanagh DPJ, Rink MR, Weston CJ, Drury NE, Kalia N. Targeting IL-36 improves age-related coronary microcirculatory dysfunction and attenuates myocardial ischemia/reperfusion injury in mice. JCI Insight. 2022 Mar 8;7(5):e155236.
26. Baker KJ, Buskiewicz E, Finucane M, Chelliah A, Burke L, Houston A, Brint E. IL-36 expression is increased in NSCLC with IL-36 stimulation of lung cancer cells promoting a pro-tumorigenic phenotype. Cytokine. 01 Mayıs 2023;165:156170.
27. Pan QZ, Pan K, Zhao JJ, Chen JG, Li JJ, Lv L, Wang DD, Zheng HX, Jiang SS, Zhang XF, Xia JC. Decreased expression of interleukin-36α correlates with poor prognosis in hepatocellular carcinoma. Cancer Immunol Immunother. 01 November 2013;62(11):1675-85.
28. Chen F, Qu M, Zhang F, Tan Z, Xia Q, Hambly BD, Bao S, Tao K. IL-36 s in the colorectal cancer: is interleukin 36 good or bad for the development of colorectal cancer? BMC Cancer. 03 Fabruary 2020;20(1):92.
29. Wang X, Zhao X, Feng C, Weinstein A, Xia R, Wen W, Lv Q, Zuo S, Tang P, Yang X, Chen X, Wang H, Zang S, Stollings L, Denning TL, Jiang J, Fan J, Zhang G, Zhang X, Zhu Y, Storkus W, Lu B. IL-36γ Transforms the Tumor Microenvironment and Promotes Type 1 Lymphocyte-Mediated Antitumor Immune Responses. Cancer Cell. 14 September 2015;28(3):296-306.
30. Chen Y, Sun J, Huang Y, Liu Y, Liang L, Yang D, Lu B, Li S. Targeted codelivery of doxorubicin and IL-36γ expression plasmid for an optimal chemo-gene combination therapy against cancer lung metastasis. Nanomedicine: Nanotechnology, Biology and Medicine. 01 Jan 2019;15(1):129-41.
31. Le N, Luk I, Chisanga D, Shi W, Pang L, Scholz G, Mariadason J, Ernst M, Huynh J. IL-36G promotes cancer-cell intrinsic hallmarks in human gastric cancer cells. Cytokine. 01 July 2022;155:155887.
32. Guo HZ, Guo ZH, Yu SH, Niu LT, Qiang WT, Huang MM, Tian YY, Chen J, Yang H, Weng XQ, Zhang Y, Zhang W, Hu SY, Shi J, Zhu J. Leukemic progenitor cells enable immunosuppression and post-chemotherapy relapse via IL-36–inflammatory monocyte axis. Science Advances. 08 October 2021;7(41):eabg4167.
33. Carrier Y, Ma HL, Ramon HE, Napierata L, Small C, O'Toole M, Young DA, Fouser LA, Nickerson-Nutter C, Collins M, Dunussi-Joannopoulos K, Medley QG. Inter-Regulation of Th17 Cytokines and the IL-36 Cytokines In Vitro and In Vivo: Implications in Psoriasis Pathogenesis. Journal of Investigative Dermatology. 01 Dec 2011;131(12):2428-37.
34. Blauvelt A. Safety of secukinumab in the treatment of psoriasis. Expert Opin Drug Saf. October 2016;15(10):1413-20.
35. Chiricozzi A, Guttman-Yassky E, Suárez-Fariñas M, Nograles KE, Tian S, Cardinale I, Chimenti S, Krueger JG. Integrative Responses to IL-17 and TNF-α in Human Keratinocytes Account for Key Inflammatory Pathogenic Circuits in Psoriasis. Journal of Investigative Dermatology. 01 March 2011;131(3):677-87.
36. Coussens LM, Werb Z. Inflammation and cancer. Nature. 2002; 420:860–7.
37. Zhang Q, Liu S, Ge D, Xue Y, Xiong Z, Abdel-Mageed AB, Myers L, Hill SM, Rowan BG, Sartor O, Melamed J, Chen Z, You Z. Interleukin-17 promotes formation and growth of prostate adenocarcinoma in mouse models. Cancer Res. 2012; 72:2589– 99.
38. Wu S, Rhee KJ, Albesiano E, Rabizadeh S, Wu X, Yen HR, Huso DL, Brancati FL, Wick E, McAllister F, Housseau F, Pardoll DM, Sears CL. A human colonic commensal promotes colon tumorigenesis via activation of T helper type 17 T cell responses. Nat Med. 2009; 15:1016–22.
39. Wang L, Yi T, Zhang W, Pardoll DM, Yu H. IL-17 enhances tumor development in carcinogeninduced skin cancer. Cancer Res. 2010; 70:10112–20.
40. Novitskiy SV, Pickup MW, Gorska AE, Owens P, Chytil A, Aakre M, Wu H, Shyr Y, Moses HL. TGF-beta Receptor II Loss Promotes Mammary Carcinoma Progression by Th17 Dependent Mechanisms. Cancer Discov. 2011; 1:430–41.
41. Xu B, Guenther JF, Pociask DA, Wang Y, Kolls JK, You Z, Chandrasekar B, Shan B, Sullivan DE, Morris GF. Promotion of lung tumor growth by interleukin-17.

Am J Physiol Lung Cell Mol Physiol. 2014; 307:L497–508.
42. McAllister F, Bailey JM, Alsina J, Nirschl CJ, Sharma R, Fan H, Rattigan Y, Roeser JC, Lankapalli RH, Zhang H, Jaffee EM, Drake CG, Housseau F, Maitra A, Kolls JK, Sears CL, Pardoll DM, Leach SD. Oncogenic Kras activates a hematopoietic-to-epithelial IL-17 signaling axis in preinvasive pancreatic neoplasia. Cancer Cell. 2014; 25:621–37.
43. Zhang Q, Liu S, Parajuli KR, Zhang W, Zhang K, Mo Z, Liu J, Chen Z, Yang S, Wang AR, Myers L, You Z. Interleukin-17 promotes prostate cancer via MMP7-induced epithelial-to-mesenchymal transition. Oncogene. Fabruary 2017;36(5):687-99.
44. Numasaki M, Fukushi J, Ono M, Narula SK, Zavodny PJ, Kudo T, Robbins PD, Tahara H, Lotze MT. Interleukin-17 promotes angiogenesis and tumor growth. Blood. 2003; 101:2620–7.
45. Kryczek I, Wei S, Szeliga W, Vatan L, Zou W. Endogenous IL-17 contributes to reduced tumor growth and metastasis. Blood. 09 July 2009;114(2):357-9.
46. Chen J gao, Xia J chuan, Liang X ting, Pan K, Wang W, Lv L, Zhao JJ, Wang OJ, Li YQ, Chen S, He J, Huang LX, Ke ML, Chen YB, Ma HQ, Zeng ZW, Zhou ZW, Chang AE, Li Q. Intratumoral Expression of IL-17 and Its Prognostic Role in Gastric Adenocarcinoma Patients. Int J Biol Sci. 11 January 2011;7(1):53-60.
47. Benchetrit F, Ciree A, Vives V, Warnier G, Gey A, Sautès-Fridman C, Fossiez F, Haicheur N, Fridman WH, Tartour E. Interleukin-17 inhibits tumor cell growth by means of a T-cell–dependent mechanism. Blood. 15 March 2002;99(6):2114-21.
48. Bankir M, Acik DY. IL-17 and IL-23 levels in patients with early-stage chronic lymphocytic leukemia. North Clin Istanb. 20 November 2020;8(1):24-30.
49. Tang D, Niu Q, Jiang N, Li J, Zheng Q, Jia Y. Increased frequencies of Th17 in the peripheral blood of patients with chronic lymphocytic leukemia: A one year follow-up. Pak J Med Sci. 2014;30(5):1128-33.
50. Alexandrakis MG, Pappa CA, Miyakis S, Sfiridaki A, Kafousi M, Alegakis A, Stathopoulos EN. Serum interleukin-17 and its relationship to angiogenic factors in multiple myeloma. European Journal of Internal Medicine. 01 October 2006;17(6):412-6.
51. Lemancewicz D, Bolkun L, Jablonska E, Czeczuga-Semeniuk E, Kostur A, Kloczko J, Dzieciol J. The role of Interleukin-17A and Interleukin-17E in multiple myeloma patients. Med Sci Monit. 01 January 2012;18(1):BR54-9.