Original Investigation
Orijinal Araştırma

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Effects of interleukin-12/23 inhibitors and interleukin-17 inhibitors on myocardial functions in patients with severe psoriasis

Şiddetli psoriazisli hastalarda interlökin-12/23 ve interlökin-17 inhibitörlerinin miyokardiyal fonksiyonlar üzerine etkileri

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Abstract

Background and Design: Systemic inflammation, which is involved in the pathogenesis of psoriasis, has been associated with the development of systemic diseases such as metabolic syndrome and cardiovascular disease. Without prospective data, the relationship between biological therapies and myocardial function in patients with severe psoriasis remains unclear. This study aimed to evaluate myocardial function changes through various parameters in psoriasis patients undergoing biological therapy for 12 months.
Materials and Methods: Patients were evaluated at the beginning of treatment and after 12 months using transthoracic echocardiography to assess systolic and diastolic heart functions.
Results: A total of 39 patients (20 males, 19 females) with a mean age of 44.28±13.54 years were included. All treatment groups significantly decreased psoriasis activity and severity index scores after 12 months (p<0.001). No significant changes in biochemical metabolic parameters were observed in any groups during the first year of treatment. A significant improvement in left ventricular global strain was observed in the ustekinumab, secukinumab, and ixekizumab groups compared to baseline (p<0.001, p=0.005, and p<0.001, respectively). A significant improvement in the E/e' ratio was noted in the ustekinumab and ixekizumab groups, but no change was found in the secukinumab group (p=0.017, p=0.010, and p=0.980, respectively).
Conclusion: This study observed improvements in systolic and diastolic cardiac functions in patients with severe psoriasis treated with anti-interleukin-12/23 (IL-12/23) inhibitors and anti-IL-17 therapies.
Keywords: Psoriasis, biologics, myocardial functions

Öz

Amaç: Psoriazis patogenezinde yer alan sistemik enflamasyon; metabolik sendrom, kardiyovasküler hastalıklar gibi birçok sistemik hastalığın gelişimi ile ilişkilendirilmiştir. Prospektif verilerin olmamasından dolayı, şiddetli hastalıkta biyolojik tedavilerin miyokard fonksiyonlarının ilişkisi belirsizliğini koruyor. Bu çalışmanın amacı, 12 ay boyunca biyolojik tedavi kullanan psoriazis hastalarında miyokardiyal fonksiyonların değişikliklerini ortaya koymaktır.
Gereç ve Yöntem: Hastalarda tedavinin başlangıcında ve tedaviden 12 ay sonra transtorasik ekokardiyografi ile kalbin sistolik ve diyastolik fonksiyonları değerlendirildi.
Bulgular: Çalışmaya yaş ortalaması 44,28±13,54 yıl olan 20 erkek, 19 kadın olmak üzere toplam 39 hasta dahil edildi. On iki aylık tedavi sonunda tüm tedavi gruplarında psoriazis alan ve şiddet indeksi skorunda anlamlı düşüş vardı (p<0,001). Tedavinin ilk yılında gruplarda biyokimyasal metabolik parametrelerde anlamlı değişiklik gözlenmedi. Ustekinumab, secukinumab ve iksekizumab gruplarında tedavi sonrası sol ventrikül global strain değerinde başlangıca göre anlamlı iyileşme gözlendi (sırasıyla; p<0,001, p=0,005 ve p<0,001). Ustekinumab ve iksekizumab gruplarında E/e' oranlarında anlamlı iyileşme görülmesine rağmen secukinumab grubunda fark yoktu (sırasıyla; p=0,017, p=0,010 ve p=0,980).
Sonuç: Şiddetli psoriazisli hastalarda anti-interlökin-12/23 (IL-12/23) inhibitörü ve anti-IL-17 inhibitörleri ile 12 aylık tedavi sonrası diyastolik ve sistolik fonksiyon bozukluğu dahil olmak üzere miyokard fonksiyon bozukluğunda iyileşme gözlenmiştir.
Anahtar Kelimeler: Psoriazis, biyolojikler, miyokardiyal fonksiyonlar

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Introduction

Psoriasis is a chronic, immune-mediated disease triggered by polygenic predisposition and environmental factors, affecting approximately 2% of the global population[1]. It is increasingly recognized as more than just a skin disease[2]. Systemic inflammation, which plays a role in the pathogenesis of psoriasis, has been linked to the development of conditions such as metabolic syndrome, cardiovascular disease (CVD), and psoriatic arthritis (PsA).

The "psoriatic march," described by Boehncke et al.[2], suggests that systemic inflammation in psoriasis leads to insulin resistance, endothelial dysfunction, and myocardial infarction. The inflammatory mediators involved include tumor necrosis factor-alpha (TNF-α), interleukin-1b (IL-1b), IL-6, IL-12, IL-17, and IL-23, which are primarily released by activated type 1 and type 17 helper T cells (Th-17) and dendritic cells[3]. Elevated levels of IL-17A have also been observed in patients with acute coronary syndromes.

Biological therapies, which target systemic inflammation at various stages, are widely used to treat moderate to severe psoriasis. These treatments are believed to lower the risk of metabolic syndrome and CVD, much like they do for psoriasis itself. In this study, we aim mainly to assess myocardial dysfunction in psoriasis patients undergoing biological therapy over 12 months and assess the metabolic parameters changes.

Materials and Methods

This study included 80 patients aged 18 to 65 years diagnosed with severe psoriasis and treated with biologics at our department of dermatology. Patients who interrupted treatment for at least 3 months due to the coronavirus disease-2019 (COVID-19) pandemic were excluded from the study. A total of 39 patients who had been treated with ustekinumab (n=15), secukinumab (n=12), or ixekizumab (n=12) at standardized doses for 12 months were analyzed. Biological therapies, which target systemic inflammation at various stages, are widely used to treat moderate to severe psoriasis. These treatments are believed to lower the risk of metabolic syndrome and CVD, much like they do for psoriasis itself. In this study, we aim mainly to assess myocardial dysfunction in psoriasis patients undergoing biological therapy over 12 months and assess the metabolic parameters changes.

Demographic characteristics, disease-related characteristics, comorbidities, psoriasis activity and severity index (PASI), and body mass index (BMI) (kg/m^2) were recorded-a dermatologist assessed psoriasis severity. We performed laboratory tests, including serum total cholesterol, low-density lipoprotein cholesterol, high-density lipoprotein cholesterol, fasting blood glucose, erythrocyte sedimentation rate, and C-reactive protein. Patients were examined at baseline and after 12 months of treatment.

Using transthoracic echocardiography, cardiac systolic and diastolic functions were assessed at the beginning and end of the 12-month treatment. We excluded patients with a history of ischemic heart disease, valvular heart disease, heart failure, and/or cardiac dysrhythmia, as well as those with morbid obesity, to ensure an objective evaluation of heart function.

All patients underwent echocardiographic evaluation using the Philips Epiq 7 ultrasound system (Philips Health Care, Andover, MA, USA) at baseline and after 12 months of follow-up. Left ventricular ejection fraction (EF) was measured using the modified Simpson method. Left ventricular diameters, volumes, and global longitudinal strain (LVGLS) were also assessed using speckle tracking. The peak LVGLS was calculated by averaging values from 16 segments of the left ventricular walls in the two-, three-, and four-chamber apical views. Diastolic functions were assessed through early (E) and late (A) transmitral flow velocities using pulsed-wave Doppler. The mitral annular early diastolic velocity (e') was measured via pulsed-wave tissue Doppler from the lateral wall of the left ventricle. The E/e' ratio was calculated to assess diastolic function. All measurements were conducted by an experienced cardiologist blinded to the treatment groups and clinical/laboratory variables.

Ethical approval

Informed consent was obtained from each patient prior to participation in the study. The KTU Karadeniz Technical University Faculty of Medicine Ethics Committee granted ethical approval before the study commenced (approval number: 5, date: 24.10.2022).

Statistical Analysis

Data analysis was performed using SPSS 23.0 software (IBM Corp., Armonk, New York). Results for descriptive data were expressed as number (n) and percentage (%). Categorical variables were compared using chi-square analysis. Normal distribution was assessed using the Kolmogorov-Smirnov test. Student's t-test was used to compare normally distributed continuous variables, while the Mann-Whitney U test and Kruskal-Wallis test were applied to compare non-normally distributed variables.

Results

A total of 39 patients (20 males and 19 females) with a mean age of 44.28±13.54 years and a mean disease duration of 19.28±8.8 years were included in the study. Obesity (35.9%) was the most common comorbidity, and the patients' mean BMI was 28.80±6.69. PsA was diagnosed in 25.6% of the patients. When evaluated according to the PASI, the mean initial PASI score was 14.98±7.84, and the mean PASI score decreased to 2.23±4.07 by the end of the first year. The study groups were similar in terms of sociodemographic and clinical characteristics. The sociodemographic and clinical characteristics of the patients are summarized in Table 1. In general, a high proportion of the patients had one or more classical cardiovascular and metabolic risk factors, including obesity, hypertension, and diabetes mellitus.

There was a significant decrease in the PASI score across all treatment groups by the end of the first year ($p<0.001$). No significant changes were observed in the biochemical metabolic parameters in any treatment group during the first year (Table 2).

At baseline, no significant differences were found in left ventricular diameters, systolic functions (EF and LVGLS), or diastolic parameters (E, A, E/e') among the patients. After 12 months of treatment, no significant changes were observed in EF, left ventricular diameters, and E and A values across all drug groups. However, there was a significant improvement in LVGLS values.

Specifically, a significant improvement in LVGLS was observed in the ustekinumab, secukinumab, and ixekizumab groups compared to baseline ($p<0.001$, $p=0.005$, and $p<0.001$, respectively). Additionally, a

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Table 1. The sociodemographic and clinical characteristics of the patients

	Total (n=39)	Ustekinumab, (n=15)	Secukinumab, (n=12)	Ixekizumab, (n=12)
Sex (%)				
Male	20 (48.7)	7 (46.7)	6 (50.0)	7 (58.3)
Female	19 (51.3)	8 (53.3)	6 (50.0)	5 (41.7)
Age (year)	44.28±13.54	43.53±16.39	41.33±13.84	43.58±12.40
BMI	28.80±6.69	28.91±9.36	28.42±4.41	29.03±4.82
Smoker (%)	10 (25.6)	1 (6.7)	6 (50.0)	3 (25.0)
Duration of disease (year)	19.28±8.8	19.53±9.37	17.50±6.58	19.17±10.37
PASI score	14.98±7.84	13.96±5.05	18.11±11.65	13.73±4.76
Comorbidities (%)				
Obesity	14 (35.9)	5 (33.3)	4 (33.3)	5 (41.7)
Psoriatic arthritis	10 (25.6)	1 (6.7)	5 (41.7)	4 (33.3)
Diabetes mellitus	6 (15.7)	1 (6.7)	-	5 (41.7)
Hypertension	3 (7.7)	2 (13.3)	-	1 (8.3)
Cardiovascular disease	1 (2.6)	-	1 (8.3)	-

BMI: Body mass index, PASI: Psoriasis activity and severity index

Table 2. The changes of biochemical metabolic parameters in treatment groups

	Ustekinumab			Secukinumab			Ixekizumab		
	Baseline	12 mo	p	Baseline	12 mo	p	Baseline	12 mo	p
PASI	13.98	7.62	<0.001	10.12	3.00	<0.001	13.73	1.10	<0.001
Fasting plasma glucose	100	97.54	0.50	90.67	94.50	0.50	119	110	0.40
HOMA-IR	10.14	10	0.55	7.43	7.81	0.55	13.50	11.03	0.33
HDL-cholesterol, mg/dL	53.27	40	0.51	45.58	45.50	0.51	47.50	47.73	0.78
LDL-cholesterol, mg/dL	129.53	129.77	0.88	118.67	117.70	0.88	122.92	127.93	0.67
Total cholesterol, mg/dL	203.2	203.05	0.89	193.08	198.56	0.89	201.83	212.82	0.35
Triglycerides, mg/dL	141.07	147.19	0.84	139	144.27	0.84	152.42	179	0.23
CRP, mg/dL	3.61	2.84	0.49	8.86	5.00	0.53	5.33	3.82	0.70
ESR, (mm/s)	14.2	10.36	0.37	19.26	18.81	0.23	15.33	13.33	0.37
Leukocyte, uL	8.14	7.70	0.37	8.14	7.70	0.68	7.31	6.68	0.23

PASI: Psoriasis activity and severity index, HOMA-IR: Homeostatic Model Assessment for Insulin Resistance, HDL: High-density lipoprotein cholesterol, LDL: Low-density lipoprotein cholesterol, CRP: C-reactive protein, ESR: Erythrocyte sedimentation rate

significant improvement in the E/e' ratio was seen in the ustekinumab and ixekizumab groups, although no significant change was noted in the secukinumab group (p=0.017, p=0.010, and p=0.980, respectively). There was no significant difference in the improvement of LVGLS between the treatment groups.

The echocardiographic parameters of the patients in the study according to the treatment groups are summarized in Figure 1a, b.

Discussion

Our study showed improvements in systolic dysfunction markers among all patients treated with IL-12/23 inhibitors and anti-IL-17 therapies, with no significant differences between the study groups. A notable improvement in diastolic dysfunction markers was seen in the IL-12/23 inhibitors and the ixekizumab group, an IL-17 inhibitor, but not in the secukinumab group.

Large-scale epidemiological studies have shown that CVD is a major cause of mortality in patients with psoriasis. The disease's duration and severity are associated with increased CVD risk. The IL-23/Th-17 axis plays a crucial role in the pathophysiology of psoriasis, where the upregulation of this pathway, along with other inflammatory cytokines, contributes to a "pro-inflammatory state" in psoriasis patients. Elevated levels of IL-23 and IL-17 have been linked to myocardial damage, stroke, and diabetes[4,5].

Patients with psoriasis have impaired longitudinal myocardial deformation showed by impaired GLS compared with healthy controls. Studies[4,5] have shown that the expression of IL-17A and IL-6 is increased in psoriasis patients, and it has been shown that this situation is associated with endothelial dysfunction and myocardial ischemia.

In literature studies[6,7], treatment with anti-IL-12/23 and anti-IL-17 therapies for more than one year is associated with a reduction in coronary artery disease incidences compared to non-biologics. In the study of Ahlehoff et al.[8], similar to our study, it was revealed that there were significant improvements in the systolic and diastolic functions of the heart with biological therapies, including TNF inhibitors and IL-

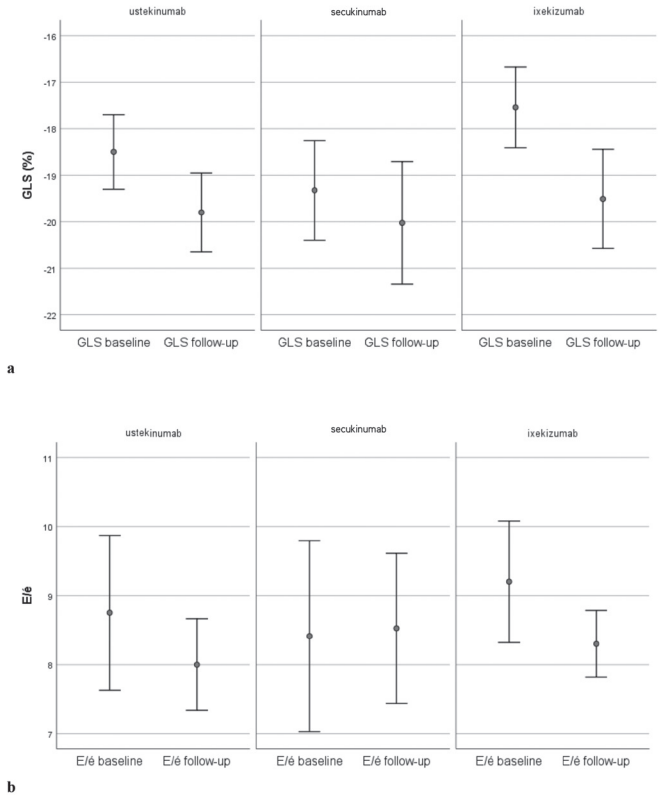

Figure 1. (a, b) The echocardiographic parameters of systolic and diastolic functions of the patients according to the treatment groups
GLS: Global longitudinal strain

12/23 inhibitors, and no changes were observed in the biochemical metabolic parameters.

In the study of Ikonomidis et al.[7], improvements were observed in the systolic and diastolic functions of the heart in ustekinumab users, compared with anti-TNF-α and cyclosporine, anti-IL-12/23 treatment resulted in a more remarkable improvement of GLS; that shows systolic functions of myocard. Makavos et al.[6] showed that psoriatic patients improved GLS and LV twisting-untwisting indices after anti-IL-17A treatment compared with cyclosporine. Brezinski et al.[9] showed in a systematic review that TNF inhibitors improve endothelial function in psoriasis and PsA.

The follow-up period in our study was 12 months, similar to the study of Makavos et al.[6], and more extended than the study of Ahlehoff et al.[8] of 3 months and Ikonomidis et al.[7], which reported 4 months.

Study Limitations

One of the main limitations of this study is the relatively small sample size (n=39). The limited number of patients in each treatment group, particularly, may complicate the assessment of statistical significance regarding treatment efficacy. Additionally, the follow-up period of 12 months restricts the ability to observe long-term outcomes, and extended monitoring would be beneficial. These limitations constrain the generalizability of the findings and make it challenging to draw definitive conclusions about the treatment effects. Our study suggests that the observed cardiac improvements during the follow-up period may indicate potential positive cardiovascular outcomes. Future research with larger sample sizes and longer follow-up durations must validate these findings.

Conclusion

This study observed improvements in systolic and diastolic cardiac functions in psoriasis patients treated with IL-12/23 inhibitors and anti-IL-17 therapies. Notably, improvements in GLS parameters support the potential beneficial effects of these biological treatments on cardiac functions. However, due to the small sample size and the limited number of patients in each treatment group, definitive conclusions about the overall efficacy cannot be drawn. More extensive studies with extended follow-up periods are needed to confirm these results. Nevertheless, the findings suggest that IL-12/23 inhibitors and anti-IL-17 therapies may positively affect cardiac function in psoriasis patients.

Ethics

Ethics Committee Approval: The KTU Karadeniz Technical University Faculty of Medicine Ethics Committee granted ethical approval before the study commenced (approval number: 5, date: 24.10.2022).

Informed Consent: Informed consent was obtained from each patient prior to participation in the study.

Footnotes

Authorship Contributions

Concept: L.B.S., B.A., Design: L.B.S., D.A.A., S.Y., Data Collection or Processing: L.B.S., M.Ş., B.A., D.A.A., Analysis or Interpretation: L.B.S., M.Ş., B.A., S.Y., Literature Search: L.B.S., B.A., D.A.A., S.Y., Writing: L.B.S., M.Ş., D.A.A., S.Y.

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