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Monocyte to High-Density Lipoprotein Cholesterol Ratio Decreased in Patients with Psoriasis Treated with Ixekizumab

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ABSTRACT

Background: Monocyte to high-density lipoprotein cholesterol ratio (MHR) is a novel inflammatory biomarker which has been associated with cardiovascular diseases. **Objective:** To study MHR in patients with psoriasis treated with biological agents. **Methods**: Between April 2019 and August 2022, MHR was retrospectively evaluated in patients with psoriasis before and 3 months after treatment with infliximab, adalimumab, etanercept, ixekizumab, secukinumab, and ustekinumab in a university hospital in Ankara, Turkey. **Results:** This study included 128 patients, 53 females and 75 males. 39 (30.5%) patients were treated with infliximab, 26 (20.3%) with adalimumab, 8 (6.3%) with etanercept, 18 (14.1%) with ixekizumab, 12 (9.4%) with secukinumab, and 25 (19.5%) with ustekinumab. The median MHR was 0.0127 (0.0086–0.0165) in females and 0.0146 (0.0119–0.0200) in males (p = 0.011). The median MHR decreased after treatment with adalimumab, ixekizumab, secukinumab, and ustekinumab, whereas it increased after treatment with infliximab and etanercept (p = 0.790, p = 0.015, p = 0.754, p = 0.221, p = 0.276, p = 0.889, respectively). **Conclusion:** MHR significantly decreased in patients with psoriasis after treatment with ixekizumab. Since high MHR levels have been associated with poor clinical outcomes in patients with cardiovascular diseases, ixekizumab might have a positive impact in the treatment of psoriasis patients who had cardiovascular diseases. We suggest that MHR may be useful both in establishing appropriate biological agent treatment and in the follow-up of patients with psoriasis treated with biological agents. (REV INVEST CLIN. 2023;75(4):187-92)

Keywords: Biological agents. Cardiovascular diseases. High-density lipoprotein cholesterol. Monocyte. Psoriasis.

INTRODUCTION

Psoriasis is an immune-mediated chronic skin disease with a prevalence of approximately 2–3% worldwide[1]. Psoriatic arthritis may accompany in up to 30% of the patients[2]. Patients with psoriasis tend to have systemic comorbidities such as cardiovascular diseases, diabetes, hypertension, hypercholesterolemia, and psychological disorders[2,3]. Biological agents which are effective in the management of psoriasis target certain inflammatory cytokines and modify immune system[4]. It has been suggested that early treatment of psoriasis

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with biological agents might prevent psoriasis comorbidities such as psoriatic arthritis, cardiovascular diseases, and metabolic disorders[2].

Monocyte to high-density lipoprotein (HDL) cholesterol ratio (MHR) has been reported as a novel biomarker which indicated systemic inflammation and oxidative stress[5]. It has been suggested that MHR was a good indicator of inflammation since it may present both inflammatory and pro-oxidant activities of monocytes and anti-inflammatory functions of HDL cholesterol[6]. MHR has been associated with various inflammatory disorders such as cardiovascular diseases, hypertension, metabolic syndrome, and psychological diseases[5,7,8]. MHR has also been used to predict vascular damage in patients with diabetes or prognosis in patients with cardiovascular diseases[5,9,10]. Moreover, it has been suggested that MHR might indicate inflammation in patients with psoriasis since systemic inflammation plays a crucial role in the development of psoriasis and systemic comorbidities[11]. In the light of this information, within this study, we aimed to evaluate the effect of biological agent treatment on MHR in patients with psoriasis.

MATERIALS AND METHODS

Gazi University Ethics Committee approval was obtained before this study (approval number 2022-955). Between April 2019 and August 2022, medical records of patients with psoriasis who were treated with infliximab, adalimumab, etanercept, ixekizumab, secukinumab, and ustekinumab were reviewed retrospectively. Age, gender, psoriasis type, psoriasis duration, accompanying psoriatic arthritis, systemic comorbidities, biological agent treatment, complete blood count, and biochemistry panel were evaluated. MHR was calculated as the ratio of absolute monocyte count ($\times 10^3/\mu L$) to serum level of HDL cholesterol (mg/dL), which was obtained from complete blood count and biochemistry panel. MHR was evaluated before and 3 months after the initiation of biological agent treatment. Exclusion criteria were pregnancy, lactation, acute infection, hematological diseases, and using cholesterol-lowering medicines.

Statistical analysis was performed using SPSS version 20.0. Quantitative variables were presented as mean±standard deviation or median (interquartile range) and categorical variables were presented as counts and percentages. Kolmogorov–Smirnov test was used to determine whether continuous variables were normally distributed or not. Differences between two groups were evaluated with Mann–Whitney U-test, Wilcoxon signed-rank test, and Kruskal–Wallis test. $p < 0.05$ were considered as statistically significant.

RESULTS

The study included 128 patients, 53 (41.4%) females and 75 (58.6%) males. The mean age of the patients was 51.47 ± 11.98 years (range: 20-77 years). 102 (79.7%) patients had psoriasis vulgaris, 14 (10.9%) had generalized pustular psoriasis, 9 (7%) had palmoplantar psoriasis, and 3 (2.3%) had palmoplantar pustular psoriasis. The mean psoriasis duration was 18.28 ± 11.62 years (range: 1–52 years). The mean disease duration was 19.98 ± 11.83 years in men and 15.88 ± 10.97 years in women ($p = 0.049$). 32 (25%) patients had psoriatic arthritis. The past medical history was unremarkable in 88 (68.8%) patients. However, 17 (13.3%) patients had hypertension, 12 (9.4%) had diabetes, 8 (6.3%) had coronary artery disease, 8 (6.3%) had hepatitis B carriage, 4 (3.1%) had chronic kidney disease, 3 (2.3%) had anxiety disorder, and 3 (2.3%) had hypothyroidism. 39 (30.5%) patients were treated with infliximab, 26 (20.3%) with adalimumab, 8 (6.3%) with etanercept, 18 (14.1%) with ixekizumab, 12 (9.4%) with secukinumab, and 25 (19.5%) with ustekinumab.

The median MHR was statistically significantly higher in men than in women ($p = 0.011$). The median MHR before treatment was 0.0125 (0.0081-0.0151) in patients with psoriatic arthritis and 0.0139 (0.0110-0.0198) in patients without psoriatic arthritis ($p = 0.036$). The median MHR 3 months after treatment was 0.0129 (0.0099-0.0151) in patients with psoriatic arthritis and 0.0143 (0.0109-0.0191) in patients without psoriatic arthritis ($p = 0.227$). The median MHR before treatment in patients with and without comorbidities was 0.0147 (0.0119-0.0179) and 0.0134 (0.0099-0.0229), respectively ($p = 0.141$). The median MHR after treatment in patients with and without comorbidities was 0.0142 (0.0098-0.0192) and 0.0138 (0.0109-0.0183), respectively ($p = 0.873$).

Table 1. The median MHR in treatment groups

Treatment groups	MHR, median (IQR)		p value
	Before treatment	After treatment	
TNF-α inhibitors	0.0131 (0.0105-0.0184)	0.0142 (0.0111-0.0193)	0.453
IL-17 inhibitors	0.0145 (0.0105-0.0225)	0.0140 (0.0102-0.0191)	0.184
IL-12/23 inhibitor	0.0135 (0.0094-0.0170)	0.0117 (0.0091-0.0158)	0.221

The median MHR decreased in IL-17 inhibitor and IL-12/23 inhibitor treatment groups whereas increased in TNF-α inhibitor group.
MHR: monocyte to high-density lipoprotein cholesterol ratio; IL: interleukin; IQR: interquartile range; TNF-α: tumor necrosis factor-alpha.

Table 2. The median MHR before and after treatment with infliximab, adalimumab, etanercept, ixekizumab, secukinumab, and ustekinumab

Biological agents	MHR, median (IQR)		p value
	Before treatment	After treatment	
Infliximab	0.0131 (0.0119-0.0188)	0.0163 (0.0121-0.0207)	0.276
Adalimumab	0.0136 (0.0103-0.0185)	0.0130 (0.0105-0.0184)	0.790
Etanercept	0.0104 (0.0084-0.0147)	0.0110 (0.0091-0.0131)	0.889
Ixekizumab	0.0138 (0.0099-0.0186)	0.0124 (0.0091-0.0188)	0.015
Secukinumab	0.0161 (0.0114-0.0820)	0.0149 (0.0119-0.0226)	0.754
Ustekinumab	0.0135 (0.0094-0.0170)	0.0117 (0.0091-0.0158)	0.221

Statistically significant decrease in median MHR was detected in patients with psoriasis 3 months after treatment with ixekizumab ($p = 0.015$).
MHR: monocyte to high-density lipoprotein cholesterol ratio; IQR: interquartile range.

The median MHR in all patients before and 3 months after treatment was 0.0136 (0.0102-0.0183) and 0.0138 (0.0107-0.0186), respectively ($p = 0.761$). The median MHR before treatment was the highest in patients received secukinumab. However, no statistically significant difference was detected in median MHR before treatment according to the biological agent received ($p = 0.473$). The median MHR after treatment was the highest in patients received infliximab. In addition, the median MHR after treatment was statistically significantly higher in patients received infliximab compared to patients received ustekinumab and etanercept ($p = 0.006$, $p = 0.011$, respectively). The median MHR in treatment groups such as TNF-α inhibitors, IL-17 inhibitors, and IL-12/23 inhibitor was stated in table 1. The median MHR decreased after treatment with adalimumab, ixekizumab, secukinumab, and ustekinumab, whereas it increased after treatment with infliximab and etanercept ($p = 0.790$, $p = 0.015$, $p = 0.754$, $p = 0.221$, $p = 0.276$, $p = 0.889$, respectively). The change in median MHR after treatment was 0.0013 (−0.00009-0.0024) in ixekizumab group which was statistically significant ($p = 0.015$). The median MHR before and after treatment with infliximab, adalimumab, etanercept, ixekizumab, secukinumab and ustekinumab was stated in table 2. The effect of biological agent treatment on MHR in patients with different types of psoriasis has also been evaluated and stated in table 3.

Table 3. The median MHR in patients with different types of psoriasis

Types of psoriasis	Biological agents	MHR, median (IQR)		p value
		Before treatment	After treatment	
Psoriasis vulgaris	TNF-α inhibitors	0.0132 (0.0109-0.0181)	0.0147 (0.0115-0.0196)	0.051
	Infliximab	0.0134 (0.0119-0.0187)	0.0159 (0.0122-0.0205)	0.104
	Adalimumab	0.0136 (0.0110-0.0179)	0.0144 (0.0113-0.0194)	0.575
	Etanercept	0.0104 (0.0086-0.0138)	0.0115 (0.0095-0.0157)	0.345
	IL-17 inhibitors	0.0148 (0.0124-0.0226)	0.0146 (0.0112-0.0191)	0.289
	Ixekizumab	0.0142 (0.0110-0.0186)	0.0127 (0.0101-0.0190)	0.060
	Secukinumab	0.0175 (0.0139-0.1075)	0.0150 (0.0140-0.0773)	0.953
	IL-12/23 inhibitor	0.0137 (0.0102-0.0167)	0.0116 (0.0093-0.0156)	0.115
Generalized pustular psoriasis	TNF-α inhibitors	0.0135 (0.0108-0.0296)	0.0135 (0.0093-0.0182)	0.203
	Infliximab	0.0130 (0.0102-0.0372)	0.0171 (0.0102-0.0211)	0.612
	Adalimumab	0.0140 (0.0125-0.0206)	0.0120 (0.0088-0.0125)	0.109
	Ixekizumab	0.0135 (0.0114-0.0800)	0.0106 (0.0094-0.0149)	0.109
Palmoplantar psoriasis	TNF-α inhibitors	0.0069 (0.0055-0.0900)	0.0071 (0.0058-0.0098)	0.465
	IL-17 inhibitors	0.0081 (0.0069-0.0199)	0.0102 (0.0070-0.0207)	0.273

MHR decreased in patients with psoriasis vulgaris after treatment with ixekizumab, secukinumab, and ustekinumab and in patients with generalized pustular psoriasis after treatment with ixekizumab and adalimumab. MHR: monocyte to high-density lipoprotein cholesterol ratio; IL: interleukin; IQR: interquartile range; TNF-α: tumor necrosis factor-alpha.

DISCUSSION

Monocytes have been related to chronic inflammation and thus development of skin lesions and systemic comorbidities in patients with psoriasis[12]. It has been suggested that monocytes might show increased cytokine synthesis, adhesion, and aggregation in patients with psoriasis[12,13]. The severity of psoriasis has been associated, especially with peripheral blood intermediate monocytes[12]. Nevertheless, the role of monocytes in the etiopathogenesis of psoriasis has not been fully elucidated[14]. In addition, HDL cholesterol exhibits anti-inflammatory effects and immunomodulatory functions by regulating monocytes, macrophages, lymphocytes, and dendritic cells. However, chronic inflammation may lead to deterioration in lipid metabolism. Functional and structural changes in HDL cholesterol have been reported in patients with psoriasis[15].

MHR is a novel inflammatory biomarker, especially used in cardiovascular diseases[5]. Nevertheless, a limited number of studies have investigated whether MHR indicated inflammatory status in psoriasis[11,16].

Sirin et al. reported increased MHR levels in patients with psoriasis compared to healthy individuals as well as relationship between MHR and severity of psoriasis[11]. Karabay et al. reported higher MHR levels in patients with psoriasis compared to hospital employees without an inflammatory disease. MHR was higher in patients with moderate to severe psoriasis compared to patients with mild disease[16]. On the other hand, Yamanaka et al. suggested that biological agents might be effective in the treatment of psoriasis by inhibiting monocyte and neutrophil activation[14].

Within this study, MHR was evaluated in patients with psoriasis treated with infliximab, adalimumab, etanercept, ixekizumab, secukinumab, and ustekinumab. The median MHR decreased 3 months after treatment with adalimumab, ixekizumab, secukinumab, and ustekinumab. However, statistically significant decrease in MHR was detected only in patients who received ixekizumab (p = 0.015). Since high MHR levels have been associated with poor clinical outcomes in cardiovascular diseases, ixekizumab may have a positive impact in the treatment of psoriasis patients who had cardiovascular diseases[5]. IL-17 which has a crucial role in the etiopathogenesis of psoriasis also released from T-cell infiltrated coronary artery. Therefore, it has been suggested that inhibition of IL-17 might prevent atherosclerosis[17]. On the other hand, Egeberg et al. reported neutral impact of ixekizumab treatment on factors related to cardiovascular diseases in patients with psoriasis[18].

Furthermore, cardiovascular diseases have an increased incidence in men compared to women[19,20]. However, gender differences on the risk for the development of cardiovascular diseases in patients with psoriasis have been evaluated in a few studies[20,21]. For instance, Garshick et al. reported that atherosclerotic cardiovascular diseases and deep vein thrombosis were more frequent in young female patients with psoriasis compared to male psoriasis patients[21]. Sondermann et al. reported that cardiometabolic risk factors were more common in female psoriasis patients than in males. Nevertheless, the effect of gender on relationship between psoriasis and cardiometabolic diseases has not been fully elucidated[22]. Within this study, the median MHR was statistically significantly higher in male patients with psoriasis than in females (p = 0.011). The high MHR levels in male patients may be related to the longer psoriasis duration in males than in females. Taking into consideration that MHR has been related to cardiovascular diseases, our result may indicate higher risk in male psoriasis patients for cardiovascular diseases than in female psoriasis patients.

Early treatment of psoriasis decreases inflammatory load and thus may have a protective role from cardiometabolic diseases. However, no inflammatory biomarker has been widely accepted to be used in the course of psoriasis[23]. Within this study, MHR significantly decreased in patients with psoriasis after treatment with ixekizumab. Since high MHR levels have been associated with poor prognosis in patients with cardiovascular diseases[16], ixekizumab may have a positive impact in the treatment of psoriasis patients who have cardiovascular diseases. This study is unique that the effect of biological agent treatment on MHR has been evaluated in patients with psoriasis. We suggest that MHR may be useful both in establishing appropriate biological agent treatment and in the follow-up of patients with psoriasis treated with biological agents.

REFERENCES

1. Damiani G, Bragazzi NL, Aksut CK, Wu D, Alicandro G, McGonagle D, et al. The global, regional, and national burden of psoriasis: results and insights from the global burden of disease 2019 study. Front Med (Lausanne). 2021;8:743180.
2. Felix PA, Sampaio AL, Silva BL, Viana AL. Early intervention in psoriasis: where do we go from here? Front Med (Lausanne). 2022;9:1027347.
3. Bu J, Ding R, Zhou L, Chen X, Shen E. Epidemiology of psoriasis and comorbid diseases: a narrative review. Front Immunol. 2022; 13:880201.
4. Brownstone ND, Hong J, Mosca M, Hadeler E, Liao W, Bhutani T, et al. Biologic treatments of psoriasis: an update for the clinician. Biologics. 2021;15:39-51.
5. Jiang M, Yang J, Zou H, Li M, Sun W, Kong X. Monocyte-to-high-density lipoprotein-cholesterol ratio (MHR) and the risk of all-cause and cardiovascular mortality: a nationwide cohort study in the United States. Lipids Health Dis. 2022;21:30.
6. Chen J, Zhong Z, Shi D, Li J, Li B, Zhang R, et al. Association between monocyte count to high-density lipoprotein cholesterol ratio and mortality in patients undergoing peritoneal dialysis. Nutr Metab Cardiovasc Dis. 2021;31:2081-8.
7. Zhou Y, Dan H, Bai L, Jia L, Lu B, Gu G, et al. Continuous positive linear association between the monocyte to high-density lipoprotein cholesterol ratio and hypertension: a cross-sectional study. Int J Hypertens. 2022;2022:8501726.
8. Wang W, Chen ZY, Guo XL, Tu M. Monocyte to high-density lipoprotein and apolipoprotein A1 ratios: novel indicators for metabolic syndrome in Chinese newly diagnosed type 2 diabetes. Front Endocrinol (Lausanne). 2022;13:935776.
9. Chen JW, Li C, Liu ZH, Shen Y, Ding FH, Shu XY, et al. The role of monocyte to high-density lipoprotein cholesterol ratio in prediction of carotid intima-media thickness in patients with type 2 diabetes. Front Endocrinol (Lausanne). 2019;10:191.
10. Ganjali S, Gotto AM Jr., Ruscica M, Atkin SL, Butler AE, Banach M, et al. Monocyte-to-HDL-cholesterol ratio as a prognostic marker in cardiovascular diseases. J Cell Physiol. 2018;233: 9237-46.

11. Sirin MC, Korkmaz S, Erturan I, Filiz B, Aridogan BC, Cetin ES, et al. Evaluation of monocyte to HDL cholesterol ratio and other inflammatory markers in patients with psoriasis. An Bras Dermatol. 2020;95:575-82.
12. Asami M, Ototake Y, Takamura N, Watanabe Y, Aihara M, Yamaguchi Y. Abnormal inflammatory traits and downregulated caveolin-1 expression in monocytes of psoriasis patients may be associated with psoriatic inflammation and atherosclerosis. J Dermatol Sci. 2022;107:65-74.
13. Golden JB, Groft SG, Squeri MV, Debanne SM, Ward NL, McCormick TS, et al. Chronic psoriatic skin inflammation leads to increased monocyte adhesion and aggregation. J Immunol. 2015;195:2006-18.
14. Yamanaka K, Umezawa Y, Yamagiwa A, Saeki H, Kondo M, Gabazza EC, et al. Biologic therapy improves psoriasis by decreasing the activity of monocytes and neutrophils. J Dermatol. 2014;41:679-85.
15. Paiva-Lopes MJ, Alves JD. Psoriasis-associated vascular disease: the role of HDL. J Biomed Sci. 2017;24:73.
16. Karabay EA, Demir D, Çerman AA. Evaluation of monocyte to high-density lipoprotein ratio, lymphocytes, monocytes, and platelets in psoriasis. An Bras Dermatol. 2020;95:40-5.
17. Patrick MT, Li Q, Wasikowski R, Mehta N, Gudjonsson JE, Elder JT, et al. Shared genetic risk factors and causal association between psoriasis and coronary artery disease. Nat Commun. 2022;13:6565.
18. Egeberg A, Wu JJ, Korman N, Solomon JA, Goldblum O, Zhao F, et al. Ixekizumab treatment shows a neutral impact on cardiovascular parameters in patients with moderate-to-severe plaque psoriasis: results from UNCOVER-1, UNCOVER-2, and UNCOVER-3. J Am Acad Dermatol. 2018;79:104-9.e8.
19. Gao Z, Xiong J, Chen Z, Deng X, Xu Z, Sun A, et al. Gender differences of morphological and hemodynamic characteristics of abdominal aortic aneurysm. Biol Sex Differ. 2020;11:41.
20. Branisteanu DE, Nicolescu AC, Branisteanu DC, Branisteanu CI, Dragoi AC, Bogdanici CM, et al. Cardiovascular comorbidities in psoriasis (Review). Exp Ther Med. 2022;23:152.
21. Garshick MS, Vaidean G, Nikain CA, Chen Y, Smilowitz NR, Berger JS. Sex differences in the prevalence of vascular disease and risk factors in young hospitalized patients with psoriasis. Int J Womens Dermatol. 2019;5:251-5.
22. Sondermann W, Deudjui DA, Körber A, Slomiany U, Brinker TJ, Erbel R, et al. Psoriasis, cardiovascular risk factors and metabolic disorders: sex-specific findings of a population-based study. J Eur Acad Dermatol Venereol. 2020;34:779-86.
23. Ramessur R, Corbett M, Marshall D, Acencio ML, Barbosa IA, Dand N, et al. Biomarkers of disease progression in people with psoriasis: a scoping review. Br J Dermatol. 2022;187:481-93.