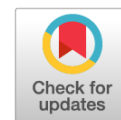


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Original study article



Comparative assessment of the dynamics of laboratory markers of endothelial dysfunction in patients with psoriasis under the influence of methotrexate and the IL-17A inhibitor netakimab

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ABSTRACT

BACKGROUND: Endothelial dysfunction, a key factor in atherosclerotic vascular damage, increases cardiovascular risk in patients with psoriasis. However, studies on clinically measurable indicators of endothelial dysfunction and their changes during systemic therapy in psoriasis are limited and inconsistent.

AIM: Comparative assessment of the clinical effect of the IL-17 inhibitor Netakimab and Methotrexate on the values of laboratory markers of endothelial dysfunction in patients with psoriasis in comparison with the dynamics of clinical efficacy indicators over 6 months of therapy.

MATERIALS AND METHODS: The study observed 66 PsA patients initially prescribed Methotrexate (Group 1: 30 patients) or Netakimab (Group 2: 36 patients). Group 1 received Methotrexate 15 mg weekly with Folic acid, while Group 2 received Netakimab 120 mg subcutaneously at weeks 0, 1, 2, then every 4 weeks. Clinical data were analyzed before, 3 months, and 6 months after treatment. Plasma levels of VEGF, endothelin-1 (En-1), and nitric oxide (NO) were measured before treatment and after 3 months.

RESULTS: In psoriasis patients, plasma levels of endothelial dysfunction markers were higher than in the control group: VEGF (19.8 [4.5; 49.4] pg/ml vs. 5.2 [0.5; 9.8] pg/ml, $p=0.004$), En-1 (286.4 [154; 439] pg/ml vs. 96.5 [32; 188] pg/ml, $p=0.002$), and NO (4.3 [2.1; 12.5] pg/ml vs. 2.2 [0.2; 5.0] pg/ml, $p=0.02$). By the third month of therapy, VEGF, En-1, and NO levels decreased, with more significant reductions in Group 2: VEGF decreased by 10.2 [8.4; 13.7] vs. 7.0 [5.6; 11.7] ($p=0.043$) and En-1 by 184.6 [167; 202] vs. 112.7 [97; 136] ($p=0.008$) in Group 1. Group 2 also showed a more pronounced decrease in PASI and NAPS1 scores at 3 and 6 months.

CONCLUSION: The work demonstrated the ability of the IL-17 inhibitor netakimab to reduce initially elevated values of laboratory markers of endothelial dysfunction.

Keywords: psoriasis; endothelial dysfunction; methotrexate; netakimab; vascular endothelial growth factor; endothelin-1; nitric oxide.

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Оригинальное исследование

Сравнительная оценка динамики лабораторных маркеров эндотелиальной дисфункции у больных псориазом под влиянием метотрексата и ингибитора ИЛ-17А нетакимаба

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АННОТАЦИЯ

Обоснование. Эндотелиальная дисфункция является одним из механизмов, лежащих в основе атеросклеротического поражения сосудистой стенки, и ассоциируется с повышенным риском развития сердечно-сосудистой патологии у больных вульгарным псориазом. В то же время исследования, посвящённые изучению клинически определяемых показателей эндотелиальной дисфункции и их динамики при системной терапии пациентов с псориазом, немногочисленны и противоречивы.

Цель исследования — сравнительный анализ воздействия ингибитора ИЛ-17 нетакимаба и метотрексата на содержание лабораторных маркеров эндотелиальной дисфункции (плазменная концентрация фактора роста эндотелия сосудов, эндотелина-1 и оксида азота) у пациентов с псориазом в сопоставлении с динамикой клинических показателей на протяжении 6 месяцев лечения.

Материалы и методы. В основу исследования положены данные динамического наблюдения за 66 больными псориазом, которым впервые назначались метотрексат (в дозе 15 мг в неделю подкожно в сочетании с приёмом фолиевой кислоты по 5 мг в неделю внутрь; подгруппа 1; $n=30$) или нетакимаб (в дозе 120 мг подкожно по следующей схеме: на 0, 1 и 2-й неделях, затем 1 раз в 4 недели; подгруппа 2; $n=36$). Оценка клинической динамики проводилась до начала терапии, а также через 3 и 6 месяцев лечения. Всем пациентам проведено исследование содержания плазменных концентраций факторов роста эндотелия сосудов, эндотелина-1 и оксида азота как до начала лечения, так и по истечении третьего месяца терапии. Контрольную группу составили 20 практически здоровых добровольцев.

Результаты. У пациентов с псориазом по сравнению с контрольной группой зарегистрирована повышенная концентрация маркеров эндотелиальной дисфункции, однако к концу третьего месяца терапии отмечалось снижение их содержания в плазме крови. Различия в снижении этих показателей между началом лечения и третьим месяцем наблюдения более выражены в подгруппе пациентов, получавших нетакимаб. Анализ клинической динамики лечения показал, что у пациентов подгруппы 2 был зафиксирован более значительный прогресс по снижению индексов PASI (распространённость и тяжесть псориаза) и NAPSИ (оценка тяжести поражения ногтей при псориазе) через 3 и 6 месяцев по сравнению с пациентами группы 1.

Заключение. В работе продемонстрирована способность ингибитора ИЛ-17 нетакимаба к снижению исходно повышенных значений лабораторных маркеров эндотелиальной дисфункции.

Ключевые слова: псориаз; эндотелиальная дисфункция; метотрексат; нетакимаб; фактор роста эндотелия сосудов; эндотелин-1; оксид азота.

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BACKGROUND

The high risk of cardiovascular adverse events and the increased incidence of cardiovascular diseases in patients with psoriasis compared with the general population are currently regarded as one of the most significant consequences of systemic inflammation [1–3]. According to population-based studies, the risk of ischemic heart disease in patients with psoriasis is increased by 1.14–1.71 times [4], myocardial infarction by 1.2–1.7 times [5], and acute cerebrovascular accidents by 1.1–1.38 times [5–7]. Numerous publications in recent years indicate that impaired endothelial function in patients with psoriasis may represent one of the main mechanisms underlying early pathologic changes in arterial vessels, which in turn increase the risk of atherosclerosis and related conditions [8, 9].

In clinical practice, the degree of endothelial dysfunction is assessed using laboratory methods that determine the concentrations of substances with vasodilatory or vasoconstrictive effects that induce hypertrophy of arterial wall smooth muscle cells and promote pathologic proliferation of endothelial cells. Among the most accessible molecules for investigation are vascular endothelial growth factor (VEGF), endothelin-1 (ET-1), and nitric oxide (NO), the concentrations of which, according to several studies, are significantly elevated in the plasma of patients with severe psoriasis [10–16]. The elevation of these markers in the systemic circulation may be associated with activation of cytokines that play a key role in the pathogenesis of psoriasis (IL-17, IL-12/23, and TNF- α) [18–21]. At the same time, studies on the effects of widely used inhibitors of proinflammatory cytokines on markers of endothelial dysfunction remain limited and inconsistent [21–24].

The work aimed to perform a comparative analysis of the effects of the IL-17 inhibitor netakimab and methotrexate on laboratory markers of endothelial dysfunction (plasma concentrations of VEGF, ET-1, and NO) in patients with psoriasis in relation to changes of clinical outcomes over 6 months of treatment.

METHODS

Study Design

This was a single-center, prospective, non-randomized study.

The primary endpoint was to identify differences in pathological angiogenesis parameters after 3 months of therapy with methotrexate or netakimab.

Eligibility Criteria

Inclusion criteria: confirmed diagnosis of moderate to severe psoriasis vulgaris in the exacerbation stage with PASI > 10 and BSA > 10%; age > 18 and < 70 years.

Non-inclusion criteria: age < 18 or > 70 years; presence of psoriasis forms other than psoriasis vulgaris; acute infectious diseases; uncontrolled hypertension; chronic heart failure more severe than New York Heart Association (NYHA) functional class I; malignant neoplasms; psychiatric disorders; use of systemic drugs for the treatment of psoriasis (psoriatic arthritis) other than methotrexate (e.g., leflunomide, sulfasalazine, cyclosporine, acitretin, Janus kinase inhibitors, biologic disease-modifying antirheumatic drugs); use of topical agents (e.g., glucocorticoids, calcineurin inhibitors, vitamin D analogues) within 2 weeks before examination; phototherapy within the past 2 months.

Exclusion criterion: refusal to participate in the study.

Study Setting

The study was conducted at the Multidisciplinary Clinical Hospital of St Luke, V.I. Vernadsky Crimean Federal University.

Study Duration

The study was conducted between 2022 and 2023.

Intervention

Depending on the selected systemic therapy for psoriasis, patients received subcutaneous methotrexate at an initial dose of 10 mg per week, which was increased to 15 mg per week after 1 month, or subcutaneous netakimab 120 mg administered at weeks 0, 1, and 2, followed by once every 4 weeks.

Main Study Outcome

The primary outcome was identifying differences in pathological angiogenesis parameters after 3 and 6 months of therapy with methotrexate or netakimab. No secondary outcomes were specified.

Outcomes Registration

All participants underwent clinical and laboratory examination, including hematologic and biochemical tests and measurement of C-reactive protein. Psoriasis severity was assessed using the Psoriasis Area and Severity Index (PASI) and Body Surface Area (BSA). In patients with nail involvement, the Nail Psoriasis Severity Index (NAPSI) was also assessed.

Plasma concentrations of VEGF and ET-1 were measured in patients with psoriasis and in the control group of healthy volunteers using enzyme immunoassay (sandwich method) on a Thermo Scientific Multiskan FC microplate photometer (Thermo Fisher Scientific, USA) with standard reagent kits (Cloud-Clone Corp, USA). Nitric oxide (NO) concentration was determined by a 2-stage diazotization reaction (Griess reaction) with formation of diazonium ions, followed by detection of the reaction products using photolorimetry with an optical filter at a wavelength of 540–570 nm (R&D Systems, USA).

Follow-up clinical assessment, including evaluation of PASI and NAPS I scores, was performed at 3 and 6 months after initiation of treatment. Laboratory assessment of endothelial dysfunction biomarkers (VEGF, ET-1, and NO) was performed after 3 months of therapy.

Statistical Analysis

The sample size was not calculated in advance.

Databases were generated using Microsoft Excel. Statistical analysis was performed with SPSS Statistics, version 11.0, and STATISTICA for Windows, version 10.0 (StatSoft Inc). Non-parametric methods were used according to distribution characteristics. The results are presented as median and interquartile range (25th–75th percentiles) (Me [25; 75]). Comparative analysis of two groups was performed using the Mann–Whitney *U* test. The strength of association between independent quantitative variables was assessed using Spearman's rank correlation (*r*). Differences were considered statistically significant at $p < 0.05$.

RESULTS

Participants

The study included 66 patients with psoriasis who were prescribed methotrexate or netakimab for the first time: 37 women and 29 men, with a median age of 45.2 [26.4–57.8] years. Disease duration ranged from 1 to 16 years.

Depending on the systemic therapy selected, patients were divided into two subgroups.

Subgroup 1 ($n = 30$) included patients who received subcutaneous methotrexate, starting at 10 mg weekly with escalation to 15 mg weekly after 1 month of therapy if well tolerated, as assessed by clinical and laboratory data. Subcutaneous methotrexate was combined with oral folic acid 5 mg weekly.

Subgroup 2 ($n = 36$), in whom methotrexate had previously been discontinued due to contraindications ($n = 5$), intolerance ($n = 22$), or lack of efficacy ($n = 9$), received monotherapy with subcutaneous netakimab at a dose of 120 mg at weeks 0, 1, and 2, then once every 4 weeks.

Median PASI and NAPS I scores in the study population were 31.5 [19.2–40.7] and 22.4 [14.9–35.2], respectively.

Comorbid cardiovascular conditions were identified in 32 patients: hypertension ($n = 25$), ischemic heart disease ($n = 8$), NYHA I heart ($n = 2$), heart valve diseases with hemodynamically significant alterations of intracardiac blood flow ($n = 3$), and diabetic angiopathies ($n = 2$).

Patients in both subgroups did not differ significantly in psoriasis severity and spread, frequency of joint, entheses, and spinal involvement, or prevalence and severity of cardiovascular disease (see Table 1).

The control group included 20 apparently healthy volunteers without skin diseases, rheumatic musculoskeletal diseases, or clinically significant cardiovascular diseases.

Primary Results

Analysis of laboratory markers of endothelial dysfunction prior to treatment demonstrated that, compared with the control group, patients with psoriasis had elevated plasma concentrations of VEGF (19.8 pg/mL [4.5; 49.4] vs. 5.2 pg/mL [0.5; 9.8]; $p = 0.004$), ET-1 (286.4 pg/mL [154; 439] vs. 96.5 pg/mL [32; 188]; $p = 0.002$), and NO (4.3 pg/mL [2.1; 12.5] vs. 2.2 pg/mL [0.2; 5.0]; $p = 0.02$).

Correlation analysis of PASI and NAPS I scores with levels of endothelial dysfunction markers revealed strong and moderate associations (in descending order) between VEGF concentration and PASI and NAPS I values, as well as between ET-1 concentration and PASI values (see Table 2).

During the 3-month treatment period, methotrexate reduced plasma VEGF and ET-1 levels, whereas netakimab reduced VEGF, ET-1, and NO simultaneously (see Table 3).

Differences in changes in endothelial dysfunction markers from baseline to 3 months were more pronounced in the subgroup of patients receiving netakimab. Specifically, VEGF concentration decreased by 10.2 [8.4; 13.7] in subgroup 2 and by 7.0 [5.6; 11.7] in subgroup 1 ($p = 0.043$), whereas ET-1 decreased by 184.6 [167; 202] and 112.7 [97; 136], respectively ($p = 0.008$).

After 3 months of treatment, patients in subgroup 2, who received subcutaneous injections of netakimab, demonstrated a more significant reduction in PASI and NAPS I scores as well as plasma C-reactive protein concentrations compared with patients in subgroup 1, who received subcutaneous methotrexate (see Table 4).

At 6 months, clinical evaluation revealed that patients in subgroup 2 maintained a more pronounced decrease in PASI and NAPS I scores (see Table 5).

Adverse Events

Throughout the study, no serious adverse reactions to subcutaneous methotrexate or netakimab requiring drug discontinuation were observed.

DISCUSSION

Summary of Primary Results

This study demonstrated the ability of methotrexate and the IL-17 inhibitor netakimab to reduce levels of all investigated biomarkers of endothelial dysfunction—VEGF, ET-1, and NO. Netakimab exerted a more pronounced effect on reducing both clinical indices of psoriasis activity and markers of endothelial dysfunction.

Interpretation

The study revealed elevated plasma concentrations of endothelial dysfunction markers in patients with psoriasis, as well as correlations between the severity and extent of skin and nail involvement and VEGF and ET-1 levels. These findings are consistent with previously reported data

Table 1. Clinical characteristics of patients who received different types of therapy

Parameter	Subgroup 1 <i>n</i> = 30 (%)	Subgroup 2 <i>n</i> = 36 (%)	<i>p</i>
Women	15 (50.0)	22 (61.1)	0.12
Men	15 (50.0)	14 (38.9)	0.10
Cardiovascular diseases	14 (46.7)	18 (50.0)	0.54
Median age, years, Me [25; 75]	49.6 [27.4; 59.8]	46.1 [23.7; 60.2]	-
PASI score, Me [25; 75]	27.6 [16.6; 35.2]	38.5 [29.5; 54.2]	0.09
Psoriatic onychodystrophy	14 (46.7)	17 (47.2)	0.73
NAPSI score, Me [25; 75]	22.1 [15.4; 36.1]	24.5 [15.5; 34.5]	0.81

Table 2. Correlation indices (*r*) between plasma concentrations of markers of endothelial dysfunction and values of clinical indices in psoriasis patients

Clinical index	VEGF	<i>p</i>	ET-1	<i>p</i>	NO	<i>p</i>
PASI	0.68	0.001	0.62	0.001	0.18	0.06
NAPSI	0.61	0.003	0.48	0.006	0.20	0.03

Note. VEGF, vascular endothelial growth factor; ET-1, endothelin-1; NO, nitric oxide.

Table 3. Changes in plasma concentrations of markers of endothelial dysfunction in patients with psoriasis after 3 months of treatment with methotrexate or netakimab (Me [25; 75])

Parameter		Subgroup 1 <i>n</i> = 30	Subgroup 2 <i>n</i> = 36
VEGF, pg/mL	Before treatment	19.6 [4.5; 34.2]	19.9 [4.2; 38.1]
	After 3 months	12.6 [3.1; 49.4]	9.7 [2.8; 25.3]
	<i>p</i>	0.02	0.009
ET-1, pg/mL	Before treatment	281.8 [161; 417]	288.3 [145; 410]
	After 3 months	169.1 [87; 221]	103.7 [56; 217]
	<i>p</i>	0.006	0.008
NO, pg/mL	Before treatment	4.3 [2.4; 11.3]	4.4 [2.0; 10.8]
	After 3 months	3.5 [1.8; 9.7]	2.0 [0.7; 7.5]
	<i>p</i>	0.008	0.008

Note. VEGF, vascular endothelial growth factor; ET-1, endothelin-1; NO, nitric oxide.

Table 4. Dynamics of clinical parameters in patients treated with methotrexate and netakimab over a 3-month period

Change vs. baseline	Subgroup 1 <i>n</i> = 30	Subgroup 2 <i>n</i> = 36	<i>p</i>
PASI	-10.8 [6.5; 14.3]	-33.0 [24.5; 37.4]	0.023
NAPSI	-2.6 [1.7; 3.3]	-9.7 [5.5; 11.4]	0.031
C-reactive protein, mg/L	-2.0 [0.5; 5.4]	-7.1 [3.5; 10.2]	0.041

Table 5. Dynamics of clinical parameters in patients treated with methotrexate and netakimab over a 6-month period

Change vs. baseline	Subgroup 1 <i>n</i> = 30	Subgroup 2 <i>n</i> = 36	<i>p</i>
PASI	-21.4 [16.5; 25.5]	-34.7 [28.7; 38.0]	0.039
NAPSI	-12.8 [8.8; 16.8]	-20.0 [17.2; 28.0]	0.035
C-reactive protein, mg/L	-6.5 [3.5; 9.5]	-7.3 [3.8; 10.0]	0.46

[14–18] and are likely explained by the involvement of these molecules in the regulation of pathological angiogenesis. Under the influence of methotrexate and netakimab, plasma concentrations of VEGF, ET-1, and NO decreased by the end of the third month of treatment, which was accompanied by reductions in PASI and NAPSİ scores and C-reactive protein levels.

The results demonstrated that treatment with the IL-17 inhibitor netakimab led to a more pronounced reduction in all studied biomarkers of endothelial dysfunction (VEGF, ET-1, and NO) at month 3 compared with methotrexate. Importantly, according to clinical efficacy data at 3 and 6 months, netakimab caused greater reduction in PASI and NAPSİ scores.

Several previous clinical trials have shown that the IL-17 inhibitor secukinumab improves endothelium-dependent flow-mediated dilation of arteries [25] and reduces the volume of non-calcified carotid plaques according to CT angiography [26]. The present study demonstrated the ability of the IL-17 inhibitor netakimab to decrease laboratory markers of endothelial dysfunction in patients with psoriasis.

Study Limitations

The study was conducted in a relatively small cohort of patients. To minimize potential bias, future multicenter studies with larger samples (≥ 1000 patients) are needed to confirm these findings.

CONCLUSION

The present study suggests that compared with methotrexate, the use of the IL-17 inhibitor netakimab results in a more pronounced reduction of elevated laboratory markers of endothelial dysfunction in patients with psoriasis.

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Thus, therapeutic approaches involving IL-17 blockade may be effective in preventing the development and progression of cardiovascular comorbidities in this patient population.

ADDITIONAL INFORMATION

Author contributions. O.A. Pritulo — hypothesis and study design, addressing ethical and organizational issues, observation of psoriasis patients, editing of the article; A.A. Petrov — collection and analysis of literature sources, patient selection, analysis of obtained results, preparation and writing of the article text; A.V. Petrov — hypothesis and study design, analysis of obtained results, editing of the article; M.Y. Marakah — statistical processing, analysis of obtained results, editing of the article. Thereby, all authors provided approval of the version to be published and agree to be accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved.

Ethics approval. The study was approved as part of the dissertation work titled “Study of the clinical and prognostic significance of angiogenesis biomarkers in psoriasis patients undergoing systemic therapy” (meeting of the Local Ethics Committee of the Crimean Federal University named after V.I. Vernadsky, protocol No. 4 dated April 12, 2022). All participants underwent the procedure of signing voluntary informed consent, including consent for the use of their data for research purposes.

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