NATIONAL AND KAPODISTRIAN UNIVERSITY OF ATHENS

DEPARTMENT OF MEDICINE

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STUDY TITLE

Effects of IL17/23 inhibitors on markers of subclinical atherosclerosis in patients with psoriasis: an observational study

STUDY PROTOCOL

Introduction

Plaque psoriasis is a chronic inflammatory disease characterized by the development of clearly demarcated, erythematous, pruritic plaques on the skin of genetically predisposed individuals. It has a worldwide incidence of 0.5–11%, with over 50% of patients developing the disease in the first three decades of life. In recent years, increasing evidence supports that psoriasis is a systemic inflammatory disease that extends beyond the skin, as it is often associated with comorbidities, including psoriatic arthritis, cardiovascular disease, metabolic syndrome, and inflammatory bowel disease, greatly affecting the quality of life of patients and mortality (1).

The pathophysiology of psoriasis is complex and has been shown to be due to inflammatory mediators of the Th1 and Th17 immune response, such as tumor necrosis factor (TNF-a), interleukin (IL) 1, IL6, IL12, IL17A, IL17F and IL23. In fact, it has been shown that these pathways are shared between psoriasis and the aforementioned comorbidities and, thus, their selective inhibition with newer biological therapies positively affects this entire disease spectrum beyond the skin (1). Regarding cardiovascular disease, current data support that psoriasis is an independent cardiovascular risk factor, as systemic inflammation can also affect the vascular endothelium in addition to the skin (2). Therefore, understanding the common pathophysiological mechanisms between psoriasis and atherosclerosis as well as studying the effect of newer biologic agents approved for the treatment of moderate/severe psoriasis on atherosclerosis may contribute to optimal management of these patients. The present study aims to highlight the effect of IL23/IL17 pathway inhibition on subclinical atherosclerosis in patients with moderate-to-severe psoriasis.

Background

Increasing evidence supports the importance of the Th17 immune response in the pathogenesis of psoriasis (3–5). Th17-differentiated T cells produce large amounts of IL17 (particularly the IL17A and IL17F isoforms), a cytokine that is significantly involved in local skin immune mechanisms and the inflammatory process of psoriasis. It has been shown that Th17 (as well as Th1) cells are found in the dermis of psoriatic lesions and produce IL17 and IL22, which in turn promote the secretion of inflammatory and antimicrobial molecules by keratinocytes. Another important cytokine is IL23, which is

responsible for the survival and expansion of Th17 cells and IL17 production (4). In combination with the above, the development of new biological agents against IL17 and IL23 for the treatment of psoriasis has highlighted in vivo the essential role of the IL23/Th17 axis in its pathogenesis (6).

Interestingly, the same axis has also been shown to play an important role in the pathophysiology of atherosclerosis (2,7). In one study, increased levels of IL23 and its receptor (IL23R) have been found in the blood and atherosclerotic plaque of patients with carotid atherosclerosis compared with healthy volunteers. Another study showed that both psoriasis patients and those with acute coronary syndrome have increased levels of Th17 immune response cytokines in the blood, including IL17A (8). The increased levels of IL17A in these patients have been correlated with the degree of platelet aggregation measured in vitro, suggesting that IL17A may promote platelet aggregation in acute coronary syndrome (9).

Taking into account the above data, it has been hypothesized that inhibition of the IL23/Th17 axis may lead to simultaneous improvement of psoriatic and concomitant atherosclerotic disease (1). To date, isolated studies have shown this association in patients receiving IL17 inhibitors for moderate or severe psoriasis. Specifically, in one study, treatment of patient for one year with an IL17 inhibitor (secukinumab) resulted in improvements in myocardial deformation, arterial elasticity, and coronary artery function, along with significant reductions in psoriasis activity and oxidative stress, findings that were not observed in patients treated with cyclosporine or methotrexate (10). In contrast, another study of patients with psoriasis did not demonstrate a significant benefit in terms of cardiovascular risk in patients treated with IL23/Th17 axis inhibitors (ustekinumab, secukinumab, ixekizumab), which was partly attributed to the short duration of treatment and follow-up (6 months) (11). Finally, in another study, biological therapy with TNF-a, IL17, and IL12/23 inhibitors was associated with reduced coronary inflammation assessed by the perivascular fat attenuation index (12).

Outcomes

The primary outcome is the assessment of the effect of treatment with an IL17 or an IL23 inhibitor on arterial stiffness in patients with moderate-to-severe psoriasis, by evaluating the pulse wave velocity (PWV) and the augmentation index normalized to 75 beats/min (AIx75) at baseline, after 24 and 52 weeks of treatment. Secondary outcomes were the comparison of change in PWV and AIx75 between the study groups and the assessment of change in psoriasis disease severity scores and in ankle-brachial index (ABI)

Patients

This observational cohort study was performed between September 2021 and September 2024. Consecutive patients with plaque psoriasis with or without psoriatic arthritis, who were monitored in the outpatient department of a tertiary academic hospital for skin diseases were included in the study if they fulfilled all of the following inclusion criteria: 1. Age ≥ 18 years; 2. Clinical diagnosis of moderate-to-severe psoriasis (Psoriasis Area Severity Index (PASI) score > 10 or Body Surface Area (BSA) >10 or Dermatology Life Quality Index (DLQI) >10) ; 3. Treatment with an IL17 inhibitor [secukinumab (Cosentyx®), ixekizumab (Taltz®), brodalumab (Kyntheum®)] or an IL23 inhibitor [risankizumab (Skyrizi®), guselkumab (Tremfya®)] or a conventional systemic agent (e.g. methotrexate, cyclosporine) or a small molecule [apremilast (Otezla®)] as monotherapy for a total of 52 weeks. The exact agent was chosen from the treatment physician of each patient, based on disease characteristics and comorbidities. Patients who did not receive biologic therapy served as a control group. Patients were not included in the if they fulfilled any of the following criteria: 1. Prior therapy with an IL17 or IL23 inhibitor; 2. Prior therapy with an TNFa-inhibitor for up to 3 months before entering the study; 3. Chronic or severe acute infections, malignancy, pregnancy or lactation

Study location

The study will be conducted at the First University Dermatology Clinic of the National and Kapodistrian University of Athens, at the "Andreas Syggros" Hospital of Athens, in

collaboration with the First University Cardiology Clinic of the National and Kapodistrian University of Athens, at the "Hippokratio" Hospital of Athens.

Materials and Methods

The enrollment of patients who will participate in the study will be carried out at the psoriasis clinic of the “Andreas Syggros” Hospital in Athens. All patients will provide written informed consent prior to enrollment in the study. The selection and administration of the biological agent will be done according to the usual practices of the psoriasis clinic based on the characteristics of the patient/disease and the international guidelines for the administration of each drug. Assessment of psoriatic disease and evaluation response will take place before the start of treatment, at week 24 and 52.

Monitoring of psoriasis

Psoriasis assessment scores including Psoriasis Area Severity Index (PASI), physician global assessment (PGA), Body Surface Area (BSA) and Dermatology Life Quality Index (DLQI) were assessed at baseline, after 24 and 52 weeks of treatment.

Monitoring of cardiovascular parameters

All patients will undergo measurement of carotid-femoral PWV, AIx75 and right and left ABI at baseline, after 24 and 52 weeks of treatment.

Statistical analysis

Statistical analysis will be performed using Statistical Package for the Social Sciences for iOS (version 29.0.2.2 IBM Corb: Armonk, NY, USA). Descriptive statistics will be used to present the patients’ characteristics. Variables with normal distribution will be reported as mean ± standard deviation (SD), while not normally distributed outcomes will be reported as median values and range. Categorical variables will be presented as frequencies and percentages. Between-group analysis will be performed using the Kruskal-Wallis Test and Student’s t-test or one-way ANOVA test. Statistical significance is determined at a two-tailed p value of 5% (0.05).

Funding

The biological agents that will be administered are approved for the treatment of moderate/severe psoriasis in Greece, so the cost of treatment will be covered by each patient's insurance after electronic prescription of each drug. The laboratory test that will be performed is part of the usual practice of monitoring treatment with biological agents, so the costs will be covered by the patient's insurance, after electronic prescription. There will be no external funding for the study.

Principal investigator

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References

1. Gisondi P, Bellinato F, Girolomoni G, Albanesi C. Pathogenesis of Chronic Plaque Psoriasis and Its Intersection With Cardio-Metabolic Comorbidities. Front Pharmacol. 2020;11(February):1–9.

2. Lockshin B, Balagula Y, Merola JF. Interleukin 17, inflammation, and cardiovascular risk in patients with psoriasis. J Am Acad Dermatol. 2018;79(2):345–52.
3. Schön MP, Erpenbeck L. The interleukin-23/interleukin-17 axis links adaptive and innate immunity in psoriasis. Front Immunol. 2018;9(JUN):1–13.
4. Bugaut H, Aractingi S. Major Role of the IL17/23 Axis in Psoriasis Supports the Development of New Targeted Therapies. Front Immunol. 2021;12(February):1–8.
5. von Stebut E, Boehncke WH, Ghoreschi K, Gori T, Kaya Z, Thaci D, et al. IL-17A in Psoriasis and Beyond: Cardiovascular and Metabolic Implications. Front Immunol. 2020;10(January):1–15.
6. Hawkes J. Discovery of the IL-23/IL-17 Signaling Pathway and the Treatment of Psoriasis. J Immunol. 2018;201(6): 1605–1613
7. Egeberg A, Gisondi P, Carrascosa JM, Warren RB, Mrowietz U. The role of the interleukin-23/Th17 pathway in cardiometabolic comorbidity associated with psoriasis. J Eur Acad Dermatol Venereol. 2020;34(8):1695–706.
8. Cheng X, Yu X, Ding Y jun, Fu Q qing, Xie J jiao, Tang T ting, et al. The Th17/Treg imbalance in patients with acute coronary syndrome. Clin Immunol. 2008;127(1):89–97.
9. Zhang S, Yuan J, Yu M, Fan H, Guo ZQ, Yang R, et al. IL-17A facilitates platelet function through the ERK2 signaling pathway in patients with acute coronary syndrome. PLoS One. 2012;7(7):1–8.
10. Makavos G, Ikonomidis I, Andreadou I, Varoudi M, Kapniari I, Loukeri E, et al. Effects of Interleukin 17A Inhibition on Myocardial Deformation and Vascular Function in Psoriasis. Can J Cardiol. 2020;36(1):100–11.
11. Marovt M, Marko PB, Pirnat M, Ekart R. Effect of biologics targeting interleukin-23/-17 axis on subclinical atherosclerosis: results of a pilot study. Clin Exp Dermatol. 2020;45(5):560–4.
12. Elnabawi YA, Oikonomou EK, Dey AK, Mancio J, Rodante JA, Aksentijevich M, et al. Association of Biologic Therapy with Coronary Inflammation in Patients with Psoriasis as Assessed by Perivascular Fat Attenuation Index. JAMA Cardiol. 2019;4(9):885–91.

PATIENT CONSENT FORM

for participation in the scientific study entitled:

"Effects of IL17/23 inhibitors on markers of subclinical atherosclerosis in patients with psoriasis: an observational study"

General information: Plaque psoriasis is a chronic inflammatory disease characterized by the development of red plaques covered with scales and can affect any area of the skin. Today we know that this disease is not limited to the skin, but can also affect other systems of the body, such as the joints, the vascular wall and the heart. Specifically, it has been shown that patients with severe psoriasis are twice as likely to develop metabolic syndrome as well as cardiovascular disease, with subsequent complications such as angina, myocardial infarction, heart failure and stroke compared to the healthy population. The newest drugs against psoriasis have proven to be very effective in treating skin lesions and improving the quality of life of patients. At the same time, there are indications that they can also improve the accompanying diseases mentioned above, including cardiovascular risk.

Aim of the study: To study the impact of systemic treatment of plaque psoriasis on subclinical atherosclerosis in patients who are going to receive an interleukin 17 or 23 inhibitor compared to those who will receive a non-biological agent.

Study design: In addition to the predefined dermatological examinations at the "A. Syggros" patients who will participate in the study will undergo a cardiological examination before the start, after 24 and 52 weeks. This examination will be carried out at the university clinic of the "Hippokrateio" Hospital of Athens, will be free of charge and will include non-invasive examinations. The results of the examinations will be used anonymously and only for the purposes of this scientific research.

Participation and withdrawal: Your consent to participate in the study is voluntary and does not deprive you of the right to withdraw it at any time you wish without any consequences for your subsequent treatment by your treating physician.

I have read the above and agree to participate in this scientific study.

Patient details
Name
Date
Signature

Physician's details
Name
Date
Signature