ΔΙΔΑΚΤΟΡΙΚΗΔΙΑΤΡΙΒΗ

ΘΕΜΑ: Clinical factors and molecular biomarkers to predict response to anifrolumab in patients with Systemic Lupus Erythematosus

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ΕΙΣΑΓΩΓΗ

Type I interferon plays a central role in the pathogenesis of systemic lupus erythematosus (SLE). Numerous studies indicate that 50-70% of SLE patients exhibit an interferon (IFN) gene signature that correlates with disease activity, severity and specific clinical manifestations[1-3]. Preclinical and clinical investigations have established Type I IFN pathway as a key therapeutic target; anifrolumab (ANI), a type I IFN receptor antagonist, was approved for the treatment of patients with moderate-to-severe SLE in 2021[4,5]. Recently, the 2023 EULAR recommendations for SLE recommend, among other immunomodulating/immunosuppressive drugs, the use of ANI as a second-line therapy for patients not responding to initial therapy, that is for patients not responding to hydroxychloroquine or who are unable to reduce glucocorticoids below acceptable doses[6]. No real-life data on the efficacy of ANI in SLE are available to date. Moreover, which SLE patients will respond to ANI in a routine clinical setting, outside the context of clinical trials, is currently unknown.

This study seeks to elucidate baseline predictive factors that predict subsets of SLE patients most likely to benefit most from type I IFN inhibition, by the use of clinical and molecular parameters.

ΣΤΟΧΟΣ

Our primary objective is to examine the efficacy of ANI across various disease manifestations in SLE patients. Additionally, we seek to uncover molecular biomarkers that may predict treatment response.

Our specific research questions include:

1) Is ANI effective in inducing remission or low disease activity?

2) What is the comparative efficacy of ANI in specific organ domains (eg. musculoskeletal, skin)?

3) What is the efficacy of ANI in relation to the number of prior therapies received.? How does the timing of ANI administration affect its efficacy?

4) What is the glucocorticoid-sparing potential ofANI?

5) Does a high baseline IFN signature predict response in rea-life clinical settings? How do patients with low interferon levels at baseline respond to ANI?

6) Is there a genetic or transcriptomic signature, above and beyond IFN signature, that predicts response to ANI?

7) What is the safety of ANI in a real-word setting

ΥΛΙΚΑΚΑΙΜΕΘΟΔΟΙ

SLE patients from the "Attikon" Lupus cohort (Attikon University Hospital) that start treatment with ANI, as per physician judgment, will be included in the study. Blood samples for genetic and transcriptomic analysis will be collected at baseline (before initiation of ANI therapy) and 6 months after. Data collected include patients' demographics, serology markers, clinical manifestations and previous treatment history. Clinical evaluation including metrology (SLEDAI, PGA, HAQ, CLASI, LUPUSQoL, SLICC/ ACR Damage Index, TJC/SJC) will be conducted at 1, 3 and 6 months. Patients will be categorized into responders and non-responders, based on standard SLE disease activity indices[7].Enrolment will be completed within 12 months. Preliminary analysis will be performed at 2 years.

IFN signature measurement as well as gene expression analysis capturing key SLE blood transcriptome signatures will be performed at baseline and 6 months in all patients, in order i) to assess whether ANI efficacy depends on the presence of a strong baseline IFN signature, ii) to evaluate intra-patient longitudinal transcriptome changes and examine whether treatment can ameliorate the identified activity/flare, severity and major organ disease signatures, and iii) to identify molecular signatures predictive of clinical response to IFN inhibition with ANI

ΣΗΜΑΣΙΑ

This study will provide data regarding real-life efficacy of ANI in a real-world setting and novel mechanistic insights regarding patient subsets that will benefit the most from treatment.

ΒΙΒΛΙΟΓΡΑΦΙΑ

1) Northcott M, Jones S, Koelmeyer R, et al. Type 1 interferon status in systemic lupus erythematosus: a longitudinal analysis. *Lupus Sci Med.* 2022;9(1):e000625. doi:10.1136/lupus-2021-000625

2) Mai L, Asaduzzaman A, Noamani B, et al. The baseline interferon signature predicts disease severity over the subsequent 5 years in systemic lupus erythematosus. *Arthritis Res Ther*. 2021;23(1):29. Published 2021 Jan 16. doi:10.1186/s13075-021-02414-0

3) Chasset F, Mathian A, Dorgham K, et al. Serum interferon-α levels and IFN type I-stimulated genes score perform equally to assess systemic lupus erythematosus disease activity. *Ann Rheum Dis*. 2022;81(6):901-903. doi:10.1136/annrheumdis-2021-221835

4) Furie RA, Morand EF, Bruce IN, et al. Type I interferon inhibitor anifrolumab in active systemic lupus erythematosus (TULIP-1): a randomised, controlled, phase 3 trial. Lancet Rheumatol. 2019;1:e208–19. doi:10.1

5) Morand EF, Furie R, Tanaka Y, et al. Trial of Anifrolumab in Active Systemic Lupus Erythematosus. *N Engl J Med*. 2020;382(3):211-221. doi:10.1056/NEJMoa1912196

6) Fanouriakis A, Kostopoulou M, Andersen J, et al. EULAR recommendations for the management of systemic lupus erythematosus: 2023 update [published online ahead of print, 2023 Oct 12]. *Ann Rheum Dis*. 2023;ard-2023-224762. doi:10.1136/ard-2023-224762

7) van Vollenhoven RF, Bertsias G, Doria A, et al. 2021 DORIS definition of remission in SLE: final recommendations from an international task force [published correction appears in Lupus Sci Med. 2022 Feb;9(1):]. *Lupus Sci Med*. 2021;8(1):e000538. doi:10.1136/lupus-2021-000538