



REVIEW

by Prof. Dr. Stoyanka Vladeva, MD

Thracian University - Stara Zagora

of a dissertation for the award of the educational and scientific degree 'Doctor'

professional field 7.1. Medicine

doctoral program "Rheumatology" Code 03.01.18.

Author: Dr. Zguro Anastasov Batalov

Form of doctoral studies: independent preparation

Department: Propaedeutics of Internal Medicine, Faculty of Medicine, Medical University - Plovdiv

Topic: "JAK / STAT SIGNAL PATH BLOCKING AS A NEW THERAPEUTIC OPPORTUNITY IN PATIENTS WITH SYSTEMIC SCLEROSIS"

Scientific adviser: Assoc. Prof. Dr. Mariela Geneva-Popova, MD

Department of Propaedeutics of Internal Medicine, Faculty of Medicine, Medical University - Plovdiv

#### 1. General presentation of the procedure and the doctoral student

The presented set of materials on paper / electronic media is in accordance with Article 115 (1) of the Procedure for Acquisition of "Doctor" in MU - Plovdiv; Regulations of MU-Plovdiv and includes the following documents:

- CV in European format with the signature of the doctoral student
- dissertation work
- abstract
- list of scientific publications on the topic of the dissertation
- list of participations in scientific forums
- photocopy of publications

2. Presentation of the doctoral student with emphasis on biographical data in connection with the procedure.

Dr. Zguro Anastasov Batalov was born on April 1, 1994 in Plovdiv. In 2013 he graduated with honors from EG "Plovdiv", and in 2019 he graduated in medicine at the Medical University - Plovdiv and received the Golden Hippocrates Award from the Rector of the Medical University of Plovdiv. Since 2021 he has been enrolled as a free doctoral student at the Department of Propaedeutics of Internal Medicine, Faculty of Medicine, Medical University - Plovdiv, headed by Assoc. Prof. Dr. Mariela Geneva-Popova, MD. Dr. Zguro Anastasov Batalov has been specializing in rheumatology since February 1, 2019 at the University Clinic of Rheumatology "Kaspela", Plovdiv.

### 3. Relevance of the topic

Progressive systemic sclerosis (MS) is part of a heterogeneous group of systemic joint diseases. The relatively high incidence of the disease, the presence of extra-systemic and systemic manifestations and the ongoing disability of patients are of significant socio-economic importance and determine the urgency of the problem. In order to avoid the early disability of patients and the initiation of inappropriate therapy, it is necessary to know as many aspects of it as possible. Lack of effective screening tests and biomarkers sometimes leads to underrecognition of the disease, delayed and ineffective treatment. The justified need to look for new, reliable biomarkers for diagnosis and new treatment to initiate remission, requires analysis of already established and new drugs that have a new therapeutic approach, obtained in a study of a large group of patients with MS.

This current issue includes systematic and comprehensive analysis of the therapy with different drugs in patients with PsA, as this would help to select the appropriate targeted therapy, which motivates the conduct of this research.

Based on the above, I believe that the topic of Dr. Zguro Batalov is relevant and important for rheumatology, as it tries to explore new, hitherto undeveloped therapeutic approaches for the treatment of patients with MSD and to accentuate on their difference with already acquaintances.

There is an actuality of the problems developed in the dissertation in scientific and scientific-applied terms.

### 4. Knowledge of the problem

The literature to which the dissertation refers includes 226 authors, presenting the leading world and our researchers related to the problem of the dissertation. The cited Bulgarian authors and articles are 14 and are related to major literary sources of Bulgarian medical literature.

The review is written on 51 pages and includes a detailed analysis of the etiopathogenesis of MSDs, the clinical characteristics of MSDs, new biomarkers for diagnosis and prognosis of the disease, assessment of target organs by immunological and instrumental methods.

The literature review concludes with a critical look at the fact that although the etiology and pathological mechanisms of MSDs are not fully understood, the disease occurs as a result of multistage and multifactorial processes involving changes in the immune system, genetic and environmental factors. The complex interrelation and parallel and mutually potentiating processes of inflammation, autoimmune activation and fibrosis, manifested to varying degrees in the course of disease evolution, determine the individual heterogeneity of clinical characteristics. The number of clinical studies in MSDs related to the role of cytokine imbalance and its relationship to objective lethality (cardiac and pulmonary involvement) is limited and no data are available in the literature on the relationship between serum and imaging biomarkers that objectify predictors. disease progression (ODA involvement).

Despite the avalanche of available therapies for MSDs, there is still no unequivocal opinion on JAK / STAT-blockade and the use of tofacitinib in patients with MSDs. There were no studies on the effect of Tofacitinib therapy on skin involvement as assessed by mRSS and high-frequency ultrasonography and on joint and tendon involvement as assessed by US10SSc score, no study of the effect of Tofacitinib therapy on lung injury as assessed by ultrasonography. Elastography-assessed splenic and hepatic impairment on digital ulcerations, no quality of life study of patients treated with Tofacitinib evaluated by patient questionnaires PROMIS 29, SHAQ, PGA VAS, CGA VAS, and a safety safety study with the drug.

Logically, the literature review concludes with the aim of the study, which was to evaluate the efficacy and safety of tofacitinib in affecting skin, joint and intra-organ involvement in patients with systemic sclerosis compared with treatment with methotrexate.

## 5. Research methodology

The chosen research methodology - research by assessment of mRSS and high-frequency ultrasonography and joint and tendon involvement, ultrasonographic

Evaluation of the monitored density of liver and spleen, evaluation of the indices PROMIS 29, SHAQ, PGA VAS, CGA VAS in patients with MSD of various therapeutic regimens allows to achieve the goal and obtain an adequate response to the tasks solved in the dissertation. .

## 6. Characteristics and evaluation of the dissertation and contributions

The dissertation is written on 185 standard typewritten pages and contains the generally accepted sections. It is illustrated with 26 figures, 16 tables and 19 appendices.

The presented dissertation is in accordance with the requirements of MU - Plovdiv for structuring and volume content - includes the following sections: Contents - 2 pages, Abbreviations used - 4 pages, Literary Review - 51 pages, Purpose and objectives - 1 page. , Patients and methods - 15 pages, Results and discussion - 51 pages, Summary - 11 pages, Conclusions - 1 page, Contributions - 2 pages, Book writing - 24 pages, Appendices - 25 pages. The abbreviations used are correctly reflected.

The literature review is in the nature of a systematic review analyzing the etiopathogenesis of PSA and the role of various biomarkers for the diagnosis and treatment of PsA. The review is comprehensive, up-to-date and focuses on the goals and objectives of the dissertation. The review is written in sufficient volume and shows that the doctoral student has in-depth knowledge of the dissertation.

The aim of the dissertation is clearly formulated and corresponds to the set tasks.

The Patients and Methods section is detailed and consistently developed. The methods of examination of the skin, internal organs and musculoskeletal system are well described.

The results are objective, illustrated with tables and figures and well interpreted using modern statistical methods - intermediate analyzes (non-parametric analysis Mann-Whitney; Kruskal-Wallis) and final analyzes (post hoc analyzes of Dunn and Dunn-Bonferroni). The graphical representation of the continuous variables is with "boxplot" diagrams, SPSS version 23.0 is used.

The conclusions are correctly reasoned and correspond to the set goal and the performed tasks. They synthesize the analysis of the survey data and their own research.

The literature reference includes enough titles from Bulgarian and foreign titles, which once again emphasizes the relevance of the issue at the global level and the need to develop it in our country.

The dissertation is written competently.

## 7. Contributions and significance of development for science and practice

The doctoral student indicated 8 contributions: 3 with original character, 5 methodical, 8 with scientific - applied, 3 with scientific - theoretical character and 2 with confirmatory character, which objectively reflect the significance of the obtained results in scientific terms and their applicability in real clinical practice.

The original contributions prove that this is the first study proving the effect of TOF therapy on skin involvement as assessed by mRSS and high-frequency ultrasonography and joint and tendon involvement as assessed by US10SSc score compared to MTX treatment in patients with SS, the assessment of liver and spleen density in patients with MSD during treatment and the first study of PROMIS 29, SHAQ, PGA VAS, CGA VAS in patients with MSD on different therapeutic regimens

Contributions of scientific and applied nature prove that digital ulcerations in SS do not increase in the treatment of SS with TOF, developed scales and indices (PROMIS 29, SHAQ, PGA VAS, CGA VAS) for SS activity can be used in routine rheumatology practice and evaluated the role of ultrasonography and elastography in patients with SS as a diagnostic method

Confirmatory contributions demonstrate that TOF treatment does not cause more severe infections (including herpes zoster virus infection) compared to MTX treatment and that the safety of TOF treatment and reported adverse reactions did not demonstrate more frequent or severe events in patients with SS treated with TOF than with those treated with MTX.

#### 8. Evaluation of the dissertation publications

6 publications were presented (3 in foreign journals and 3 in national journals) and 8 participations in scientific forums were realized. The number of scientific papers meets the quantitative criteria set out in the Regulations of MU - Plovdiv.

#### 9. Personal participation of the doctorant

The doctorant personally participated in the dissertation research, as he personally assessed the condition of the musculoskeletal system and the activity of the MSS.

#### 10. Abstract

The abstract presents the goals, tasks, results and discussion, conclusions and contributions of the dissertation in a concise, generalized form. The results are graphically illustrated for greater demonstration and presented in tabular form, where greater accuracy is required. The abstract gives a comprehensive idea of the results and contributions of the dissertation.

#### 11. Critical remarks and recommendations

I don't have

#### CONCLUSION

The dissertation contains scientific, scientific-applied and applied results, which represent an original contribution to science and meet all the requirements of the Law on the Development of Academic Staff in the Republic of Bulgaria (ZRASRB), - Plovdiv. The presented materials and dissertation results fully comply with the specific requirements adopted in connection with the Regulations of MU - Plovdiv.

The dissertation shows that the doctorant Dr. Zguro Anastasov Batalov has in-depth theoretical knowledge and professional skills in the scientific specialty "Rheumatology", demonstrating qualities and skills for independent research.

Due to the above, I confidently give my positive assessment of the research, to continue the procedure for finalizing the dissertation through public defense to obtain the educational and scientific degree "Doctor" of Dr. Zguro Anastasov Batalov in a doctoral program in Rheumatology.

June 16, 2022.

Prepared the opinion: Prof. Dr. Stoyanka Vladeva, MD

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Заличено на основание  
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