



To the Chairman of the Scientific jury,
Appointed by Order №
Of the Rector of Medical University - Plovdiv
15A, "Vasil Aprilov" blvd.
4002 Plovdiv



REVIEW

By

Prof. Mariela Geneva-Popova, MD, PhD

On

Dissertation for the attainment of educational and scientific degree of
"DOCTOR"

Field of higher education: 7. „Healthcare and sport“
Professional field: 7.1. „Medicine“
Doctoral program „Rheumatology“

Author: Stefka Kamenova Neycheva, MD

Form of doctoral studies: independent preparation

Department: Propedeutics of internal diseases „Prof. Dr. Anton Mitov“

” Compliance and persistence with biologic treatment in patients with rheumatoid arthritis among Bulgarian population“

Scientific supervisor: Assoc. Prof Rosica Karalilova, MD, PhD, DMSc

1. General presentation of the procedure

The provided set of materials on paper/electronic media is complete and in accordance with Article 70 (1) of Section I. Acquisition of the educational and scientific degree “Doctor” is in accordance with the Regulations of Medical university of Plovdiv (dated January 28, 2021), the Law on the Development of Academic Staff in the Republic of Bulgaria, its Rules and Regulations for application.

Brief biographical Information about the doctoral student:

Dr. Stefka Kamenova Neycheva was born on November 2, 1981, in Plovdiv. In 2000, she completed her secondary education at the Language High School in Plovdiv, and in 2006, she graduated in Medicine from the Medical University of Plovdiv. The doctoral student obtained a specialization in “Internal Medicine” in 2013, and in December 2016 – a specialization in “Rheumatology”. Since 2017, she has been working as a rheumatologist in the Rheumatology Department at Military Medical Academy-Sofia. From December 2022 to January 2024, Dr. Neycheva has been a free doctoral student in the Doctoral Program in Rheumatology at the department of Propedeutics of Internal Diseases. Prof. Dr. Anton Mitov, Faculty of Medicine, Medical University of Plovdiv, with training base at the Rheumatology Clinic of UMBAL “Kaspela” EAD, Plovdiv. She is proficient in Russian, German, and English.

2. Relevance of the issues addressed in the dissertation.

Rheumatoid arthritis is the most common type of arthritis, affecting 0.5-1% from the population in Europe and North America. If the disease is not treated in a timely and adequately manner, it is associated with reduced ability to work and increased risk of early mortality. The low adherence to the prescribed medication among the patients with chronic diseases is a primary and persistent issue that leads to disease progression and early invalidation of the patient. Recent therapeutic recommendations are based on “treat to target” strategy. These recommendations involve adjusting therapeutic doses, combining certain medications, or switching from one DMARD to another with the aim of achieving remission or low disease activity. “Treat to target” treatment can effectively reduce the symptoms, structural and x-ray progression and to improve the long-standing prognosis in patients with RA. To achieve these therapeutic goals, patients must strictly adhere to the therapeutic regimens prescribed by the their treating rheumatologist. Non-compliance with the therapeutic plan by the patient can result in financial burdens, disease progression and worsening of the physical impairment, in a necessity to add new medications, and in some cases the need to perform a surgical interventions.

The issue discussed in the dissertation is current and significant. The importance of the problem is underscored by the comprehensive bibliography, which includes 158 sources. Authors from many countries have attempted to analyze the treatment adherence based on the particularities of their respective populations. Their aim has been to estimate the factors influencing the compliance and persistence of bDMARDs. The published data regarding this issue in the worldwide literature are controversial. Only a few authors compare the adherence to such a wide array of biologic agents.

3. Understanding of the problem

The literature search is comprehensive, encompassing all aspects of the considered problem. All sources have been thoroughly examined. The analyzing the comparison is challenging due to the different methods used for the adherence assessment, as well as the multitude of bDMARDs being compared. This demonstrates a profound understanding of the problem and reflects the doctoral student's awareness.

An exhaustive analysis was conducted to examine the factors influencing the problem and their relationship with the disease activity, quality of life and the patient's functional capacity.

The study holds a significant scientific and practical value. Understanding of the factors that influence a patient's adherence to the prescribed treatment will assist the physicians in identifying the patients at risk for the treatment interruption. This knowledge will contribute to the development of national patient programs and strategies aimed at improving the patient's awareness about the disease, as well as providing support for both the patients and their family.

4. Advisability of the aims and objectives

The goals of the dissertation are formulated clearly and accurately. All eight determined tasks are correct in accordance with the defined objectives and are adequate for their realization.

5. Design of the study

The materials and methods are correctly selected and accurately linked to each of the determined objectives. This a retrospective study. The patients were consequently recruited; all eligible individuals were included in the study and started treatment with biologic agents between October 2014 and May 2017. The patients were followed up for the period of three years (36 months) until December 2020. In the study, the maximum sample size was targeted. A simple random sample with a relative proportion indicator of 50% was used. Assuming a population size of

2000 patients, a maximum permissible error of 7% was set, with a 95% confidence level and 80% power. The sample size obtained was 179 patients.

The protocol of the clinical study is described in detail, along with a chronological overview of the trial.

6. Characterization and Evaluation of the Dissertation Work

The presentation of the results from the original research is thorough and well-illustrated with 90 tables and 15 figures. The methods used and the results of statistical analyses are outlined in detail. The substantial volume of data is well considered and systematically organized.

In the discussion, the doctoral candidate demonstrates a strong understanding of the developed problem and an excellent ability to compare and interpret the results based on her own observations and research with those reported in the global literature.

The conclusions are clearly formulated for each individual task and collectively for the overall theme of the work. Dr. Stefka Neycheva thoroughly and comprehensively explores compliance and persistence towards different classes and subclasses of biological medications among the Bulgarian population of patients with RA. She investigates the factors that could influence adherence to prescribed treatment.

7. Contribution and Significance of the Development for Science and Practice

The development encompasses significant scientific-applied and scientific-theoretical contributions:

For the first time in Bulgaria, a comparative study on compliance and persistence towards individual biological medications among the Bulgarian population of RA patients is conducted. An attempt has been made to determine factors influencing adherence and the duration of adherence to biological therapy in RA patients, including age, gender, disease duration, monotherapy with bDMARDs or combination with MTX, and prior exposure to a biological agent. The impact of factors such as age, gender, disease duration, monotherapy with bDMARDs or combination with MTX, and previous exposure to a biological agent on disease activity, functional status, and quality of life, assessed through the DAS28-ESR, HAQ-DI, and SF-36 questionnaires, has been analyzed.

8. Evaluation of the publications related to the dissertation work.

In connection with the dissertation, three publications have been presented - one in a foreign journal with an Impact Factor for the year 2022 of 4.0 and two in national journals. The number of scientific works meets the quantitative criteria set out in the Regulations of Medical University - Plovdiv.

9. Abstract

The abstract comprises 54 pages and serves as a summary of the dissertation work. It provides an opportunity for a visually and sufficiently comprehensive understanding of the goals, tasks, results, discussion, conclusions, and contributions of the work. It reflects the main results achieved in the dissertation and is well-illustrated with tables and graphs.

10. Critical notes and recommendations


I have no critical comments or recommendations for the dissertation. The work appears to be fully completed, and the stated goals and tasks have been successfully achieved. The conclusions are logical and beneficial.

CONCLUSION

The dissertation work contains scientific and applied results that represent an original contribution to the field and comply with all the requirements of the Law for the Development of Academic Staff in the Republic of Bulgaria, the Regulation for the Implementation of the law, and the corresponding Regulation of MU - Plovdiv. The presented materials and dissertation results fully meet the specific requirements of MU - Plovdiv.

The dissertation work demonstrates that the doctoral student, Dr. Stefka Kamenova Neycheva, possesses in-depth theoretical knowledge and professional skills in the scientific specialty of rheumatology. It showcases qualities and abilities for independently conducting scientific research.

Based on the above, I confidently provide my positive assessment of the conducted research presented in the reviewed dissertation, abstract, achieved results, and contributions. I recommend to the esteemed academic jury to confer/do not confer the educational and scientific degree of 'Doctor' upon Dr. Stefka Kamenova Neycheva in the doctoral program of Rheumatology.


Reviewer: Prof. Mariela Genova-Korova, MD, PhD