STANDPOINT

by Assoc. Prof. Atanas Angelov Atanasov, MD, PhD

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of

dissertation work for the acquisition of educational and scientific degree
"DOCTOR"

in Higher Education Area 7. Health and Sports Professional area 7.1. Medicine, Specialty Internal Diseases on the topic:

STUDY OF CLINICAL ACTIVITY OF RHEUMATOID ARTHRITIS IN PATIENTS, TREATED WITH BIOLOGICAL PRODUCTS

of Dr. Tanya Kirilova Shivacheva

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with supervisor Prof. Dr. Svetoslav Georgiev, Ph.D.

By order N: P-109-249 / 30.07.2019 of the Rector of MU Varna I was elected a member of the scientific jury and accordingly with order N: P-109-350 / 14.08.2019 I was appointed to prepare standpoint on the procedure for the acquisition of the educational and scientific degree "Doctor" with candidate Dr. Tanya Kirilova Shivacheva.

Short data on the professional development and qualification of the doctoral student: Dr. Tanya Shivacheva graduated from the Medical University of Sofia in 1982. During the period 1982-1985 she worked as sections therapist, and since 1985 has been a physician at the University Hospital "St. Marina". In 1989 and 1997 Dr. Shivacheva acquired the specialty "Internal Diseases" and respectively "Rheumatology". Since 1989, Dr. Shivacheva has been an assistant at the Department of Internal Medicine at the Medical University of Varna. She conducts internal medicine exercises with medical students.

Relevance of the topic: Rheumatoid arthritis (RA) is a chronic, non-lethal disease, but patients are middle-aged, with varying degrees of disability and shorter life expectancy. Very often the disease is accompanied by other chronic diseases. Cardiovascular diseases (CVD) are the most common comorbidity in patients with RA. Only with the presence of classic risk factors it cannot be fully explained why RA patients have a higher risk of CV disease. Inflammation plays a key role in the pathogenesis of the atherosclerotic process. The higher incidence of atherosclerotic CV disease among RA patients can be explained by the concept of systemic inflammatory process that is characteristic of this joint disease.

Clear criteria for early diagnosis of RA have been established. The goals of treatment are well defined. Modern medicines are available to help remission in a significant proportion of patients. However, there is no consensus on the combined indicators for evaluating the effectiveness of the application of new therapeutic approaches. Despite treatment, patients with RA continue to have high morbidity and mortality from other causes and these are primarily CV diseases. A more comprehensive approach to patients with chronic conditions, such as RA, is obviously needed. In other chronic diseases, such as heart failure, the practice of creating multidisciplinary teams involving different medical specialties is required in some European countries.

Structure of the dissertation: The thesis of Dr. Tanya Shivacheva is designed according to the requirements of 190 pages and is illustrated with 62 figures and 33 tables. The dissertation is well balanced and includes introduction and literature review (75 pages), purpose and objectives (2 pages), material and method (21 pages), own results and discussion (59 pages), conclusions and contributions (4 pages). The bibliography contains a total of 292 sources (2 in Cyrillic), of which 32% have been published in the last 5 years. The abstract includes 40 figures and 20 tables.

Literature review: The literature review shows a very good awareness of the author on the topic. The epidemiology and social significance of the disease are discussed in detail. Particular attention has been paid of treatment strategies and goals. Various options for evaluating RA activity and the effectiveness of biological agents are discussed. It is emphasized that there are conflicting data on the efficacy of biological treatments on CV morbidity and mortality. Up-to-date data from registries and clinical trials are presented. In the second part of the review, the author discusses the problem of comorbidity in patients with RA. Submitted for data from numerous epidemiological studies in the last 50 years. A very detailed historical analysis has been made of how the prognosis of the

disease is changing with the development of therapeutic approaches in recent decades It is emphasized that patients with RA have a disproportionately higher comorbidity even at the onset of their disease. According to the author, this remains a great challenge for contemporary rheumatology. An entire chapter of the literature review focuses on the available data and evidence on the effects of major classes of drugs used in the treatment of RA, including their relationship to CV risk.

Purpose and tasks: The dissertation formulates the main objective of the scientific development as a logical continuation of the literature review: To optimize the evaluation of the clinical activity of RA in view of improved long-term prognosis of patients. Five tasks have been formulated to achieve this.

Material and Method: Dr. Shivacheva analyzes retrospectively 197 consecutive patients who have been through the diagnostic consulting cabinet at the Clinic of Rheumatology at the University Hospital "St. Marina". The indicators analyzed are: demographic; clinical features of RA; therapeutic options for the treatment of RA; clinical indicators to evaluate the safety of biological treatment; clinical indicators for evaluating RA activity; laboratory indicators for evaluating RA activity; indices for evaluating the momentary activity of RA; accompanying diseases; classic risk factors for atherosclerotic CV disease. Modern statistical methods have been used to interpret the data.

Results and Discussion:

The following are the most significant results found:

- The most common comorbidity in patients with RA is CVD. The mean age of RA debut is higher in individuals with concomitant CVD.

- The combination of RA and CV diseases is associated with more frequent use of corticosteroid therapy and higher values of inflammatory markers.

- There are no significant differences in the type and duration of biological therapy in patients with and without CV disease.

- The proportion of patients undergoing monotherapy with biological agents is significantly lower in patients with concomitant CV disease.

- In patients with RA and CV disease, the mean creatinine value was significantly higher at the end of follow-up.

- Patients with RA and CVD have a significantly higher value of the two DAS 28 variants evaluating RA activity.

- There is a significant discrepancy between the estimates of the two DAS 28 variants classifying patients in different activity categories.

- In order to determine the prognostic probability for the development of CV disease, the dissertant develops several variants of a prognostic model. Key elements in these models are: disease activity assessed by DAS 28; treatment with synthetic agents (methotrexate) and administration of corticosteroids.

As a result of the results obtained and the analysis made Dr. Shivacheva offers an easy-to-implement three-step algorithm that should be followed both in the presence and absence of concomitant CV disease. Adherence to it can be expected to lead to:

- delaying the progression of RA;

- suppression of accelerated early atherosclerosis;

- reduction of morbidity and mortality from CV diseases.

Conclusions: Conclusions meet the stated purpose and tasks. They are well formulated and logically derived from the results obtained.

Contributions: Of the contributions that have been made to the most significant, I accept:

- For the first time in Bulgaria is described also considered in dynamics picture of RA activity against the background of treatment with biological agents in real clinical practice.

- Traditional risk factors for CV disease have been analyzed in combination with factors arising from the inflammatory nature of RA and its treatment.

- An algorithm for individual care in a patient with RA has been proposed with the ultimate goal of improved quality of life and increased life expectancy.

Publications and Scientific Papers in Relation to the Thesis: In connection with the dissertation, Dr. Shivacheva submits only 2 publications. I believe that the dissertation student has the potential and material on the topic, which allows for more publications.

Critical notes:

1. Some of the sources in the bibliography are not cited according to generally accepted rules.

2. At the beginning of the abstract most of the abbreviations used in the text are missing, which creates some reading discomfort.

Conclusion: Dr. Tanya Shivacheva's dissertation treats very current issue in the field of internal diseases and in particular rheumatology and cardiology. Sufficient evidence is presented for the dependency between RA and CV diseases. At present, the problem of comorbidity in patients with chronic diseases is very topical and has been studied worldwide. Dr. Shivacheva offers a very practical algorithm for behavior that is expected to reduce the risk of CV disease in RA patients. I think so that Dr. Shivacheva's dissertation fulfills the requirements for awarding the educational and scientific degree "Doctor". This gives me reason to confidently suggest to the distinguished scientific jury to vote positively for the award of the Doctor's degree to Dr. Tanya Shivacheva.

Varna, 08.09.2019

Assoc. Prof. Atanas Angelov Atanasov, MD, PhD