

To the President  
of the Scientific Jury, appointed by  
the Rector of the Medical University,  
Varna “Prof. Dr. Paraskev Stoyanov”,  
by order NR-109-249 / 30.07.2019

## RECENSION

**By Prof. Dr. Zhaneta Georgieva Tianeva, PhD, Member of the Scientific Jury, determined by Order No. R-109-249 / 30.07.2019 of Prof. Dr. Krasimir Ivanov, MD, Rector of the Medical University “Prof. Dr. Paraskev Stoyanov”, Varna, for the acquisition of the educational and scientific degree “Doctor”, in the field of higher education 7.“Health and sports”, professional direction 7.1.“Medicine”and scientific specialty “Internal diseases”, of Dr. Tanya Kirilova Shivacheva, doctoral candidate self-study in a doctoral program in Internal Medicine, Department of Propaedeutic of Internal Diseases, Medical University Varna**

### **Biographical data:**

Dr. Tanya Kirilova Shivacheva successfully graduated from the Medical University in Sofia in 1982. Since 1985. works as a resident doctor in the Intensive Cardiology Unit of the Cardiology Clinic at St. Marina Hospital EAD Varna. In 1987 she was appointed as a resident physician at the Clinic of Rheumatology. Since 1989 she has been an assistant at the Department of Internal Medicine, Paraskev Stoyanov Medical University in Varna. She acquires specialty in internal diseases in 1989 and specialty in rheumatology in 1997.

Since the beginning of 2019 with the order of the Rector of the Medical University of Varna, Dr. Shivacheva has been enrolled as a doctoral student of independent form of study in a doctoral program "Internal diseases" with the theme of the dissertation: "*Study of clinical activity of rheumatoid arthritis in patients, treated with biological products*"

She is a member of the Society of Rheumatologists in Bulgaria

**Scientific – research activity.**

**Thesis: " Study of clinical activity of rheumatoid arthritis in patients, treated with biological products".**

The thesis is of 189 pages. The bibliographic reference is up-to-date, comprehensive and includes 264 authors, 97% of them after 2010. The literature review is detailed and problem-oriented. Doctoral candidate shows a broad knowledge of the topics discussed.

In the literature review, Dr. Shivacheva presents evidence that persistent systemic inflammation and immune dysfunction characteristic of RA play an important role in the development and acceleration of comorbidities. In patients with RA, there is an unusual cumulation of concomitant diseases with the highest proportion of cardiovascular diseases, a major cause of high mortality. Two basic principles are identified for initiating treatment for RA: early and aggressive therapy and treatment for the target. The activity of RA, the purpose of treatment, the effectiveness of biological agents, accompanying diseases and long-term prognosis in patients with RA are thoroughly analyzed and evaluated. It is argued that there is no consensus on the combined indicators for evaluating the effectiveness of therapeutic approaches and targeting molecules in daily clinical practice.

It stands out the role of inflammation as a major feature of RA, both for the progression of functional disability and for the development of a large number of comorbidities and early death; In clinical practice, the use of combination indicators reflecting the inflammatory activity of RA is allowed as a combined measure to evaluate the effectiveness of the therapy being performed. Their use allows for continued residual activity of RA, which, despite the use of expensive, biological molecules, compromises the results of treatment. This underestimated activity can be considered as a reason for the deterioration of the functional capacity of the patients and the development of concomitant cardiovascular diseases or the increased risk for them, which ultimately lead to premature death. The conclusion is that therapeutic options in RA patients should be consistent with the concomitant CVDs and their risk characteristics. In clinical practice, as a combined measure to evaluate the effectiveness of the therapy, is allowed the use of combined indicators that

reflect the inflammatory activity of RA. Their use allows the residual activity of RA to be continued, which, despite the use of expensive biological molecules, compromises the results of treatment. This undervalued activity can be seen as a reason for the deterioration of patients' functional capacity and the development of concomitant cardiovascular diseases, or the increased risk for them, which ultimately leads to premature death. The conclusion is that therapeutic options should be considered in patients with RA according to their accompanying CVD and their risk characteristics.

**The purpose of the dissertation** is clearly stated, as well as its tasks. The materials and methods presented provide validity of the results obtained to optimize the evaluation of the clinical activity of RA with a view to improving long-term prognosis of patients and analysis of the clinical activity of RA in patients undergoing treatment with biological agents with and without accompanying diseases and dependency analysis RA activity, through DAS28 (ESR) and DAS28 (CRP); It is determined forecast probability for CVD development. An algorithm is proposed to improve the clinical course of RA patients and reduce the risk of CVD. The tasks are precisely set out and accomplished precisely in scientific work.

**195 patients with RA were examined. Modern statistical methods for processing and analysis and frequency tables were used.** The relationship between two categorical variables is presented in a special type of cross-tabulation. The Pearson chi-square test or the Fisher test is used in the data analysis for qualitative variables in one-dimensional analysis. 95% confidence intervals (95% CI) for each relative risk were calculated. To summarize and compare differences in descriptive statistics in one or more factors or category variables, Compare Means is used.

**The results** are precise and accurate convincing. Discussion of the results presents a link between own results and data from the literature review. The time from the beginning of diagnosis to the start of biological treatment is analyzed. Discussed: duration of biological treatment, type of biological preparation: anti-TNF $\alpha$ ; anti -IL6; anti-CD20, clinical indicators related to the level of RA activity and the safety of patients undergoing biological treatment. The level of disease activity was interpreted as low (DAS28 <3.2), moderate and high (DAS28 > 5). Patients with DAS28 <2.6 were classified as remission patients. Criteria for responding to synthetic and / or biological therapy are proposed. Dr. Shivacheva found that the highest relative share (61.3%) of the accompanying

pathology in patients with RA had CVD, the most common of these being arterial hypertension followed by ischemic heart disease.

**The findings** of the studies are for more frequent use of corticosteroid therapy (70%), less frequent use of MTX, greater number of painful joints, higher VAS values, higher DAS28 values (ESR and CRP) which, despite favorable biological effects, remained higher throughout the period monitored, higher average RA activity throughout the study period presented in synchrony with the two variants of DAS28 (ESR) and DAS28 (CRP.) In determining the activity of RA during the follow-up, it was found that the average DAS28 activity (ESR) is higher than the average DAS28 activity (CRP) and there were significant differences in categorizing patients according to the activity on the two scales. Significant reduction of the predicted probability for the development of CVD can be achieved by: reducing the limit categorizing patients in low activity status by DAS28 (CRP)  $<2.67$  (30% reduction in predicted probability), introducing MTX into the therapeutic model, discontinuing treatment with corticosteroid at the first opportunity.

I accept and agree with the conclusions drawn and reference for the dissertation contributions

**Contributions of theoretical nature:** For the first time in Bulgaria the activity of Rheumatoid arthritis is described and thoroughly studied in dynamics, against the background of biological treatment, in real clinical practice, in different therapeutic models and according to the presence of CVD, the causes of death in them, the traditional risk factors, as well as the factors originating from the nature of RA and its treatment related to general mortality. Traditional CVD risk factors have been analyzed in combination with factors derived from the inflammatory nature of RA and its treatment in real clinical practice. The activity of RA in patients with and without CVD was analyzed and presented in synchrony with two variants of the combined DAS28 indicator. An in-depth, comprehensive and dynamic analysis of the relationships between the assessments of the two DAS28 variants and the impact of the CVD on them has been carried out.

**Contributions of practical nature:**

It is proposed introduction into daily clinical practice of an indicator representing the average activity of RA over a period of time. Optimized DAS28 (CRP) values are proposed that can be incorporated into daily clinical practice in order to: refine residual RA activity during biological

and synthetic treatments; improving the long-term prognosis of patients taking into account the added CV risk. A significant contribution to Dr. Shivacheva's dissertation is the proposed algorithm for individual care in patients with RA, with the ultimate goal of improving the prognosis of patients, improved quality of life, and improved life expectancy. The dissertation may be the basis for a prospective verification of the proposed prognostic model.

The doctoral student has published 2 articles on dissertation work. Some of the results were reported in an international forum.

**In conclusion:**

Dr. Tanya Shivacheva can be identified as a researcher, capable of independent scientific work in the area of rheumatology and internal diseases, an erudite doctor with high professionalism.

The dissertation submitted and scientific publications meet the accepted scientometric criteria provided for in the Law on the Development of the Academic Staff in the Republic Bulgaria and the Rules for the Development of the Academic Staff in the Medical University of Varna, for the acquisition of the educational and scientific degree "Doctor", in the area higher education 7."Health and sports ", professional direction 7.1." Medicine "and scientific specialty" Internal diseases ".

**I propose with confidence to the Scientific Jury Dr. Tanya Kirilova Shivacheva for the acquisition of the educational and scientific degree "Doctor" in the professional field "medicine" in the specialty "internal diseases"**

09/10/2019

Varna

Reviewer:

(Prof. Dr. G. Georgieva, PhD)