To the Scientific Jury
Designated by order № P-109-166 / 03.06.2020 of
The Rector of the Medical University Prof. Dr. P. Stoyanov
Varna

REVIEW

by Prof. Svetoslav Zhivkov Georgiev, MD, PhD

Member of the Scientific Jury regarding the Competition for the academic position of ASSOCIATE PROFESSOR in the field of higher education Health and Sports, in the professional field of Medicine and scientific specialty "Rheumatology" for the needs of the First Department of Internal Medicine, Faculty of Medicine at MU-Varna and Clinic in Rheumatology at the University Hospital "St. Marina ”EAD – Varna

Brief information about the competition:

By order № P-109-166 / 03.06.2020 of the Rector of MU-Varna I was appointed a member of the Scientific Jury. The competition was announced in the State Gazette no. 8 / 28,01,2020 Dr. Tanya Kirilova Shivacheva is the only candidate. The procedure for announcing the competition is in compliance with the requirements of the Law for development of the academic staff in the Republic of Bulgaria / 05.05.2018 and with the Regulations for development of the academic staff in MU-Varna / 22.07.2019.

Brief information about the candidate:

Tanya Kirilova Shivacheva MD graduated in medicine in 1982 at the Medical University, Sofia. She started working as Head of the Rural Health Department in 1982, and then successively worked as an intern in the intensive care unit at the Higher Medical Institute in Varna. In 1989, after a competition, she was appointed an assistant at the Department of Internal Medicine Higher Medical Institute - Varna. Since 2000 he has been chief assistant at MU-Varna. Dr. Shivacheva is fluent in English, German and Russian.

Acquired specialties and postgraduate qualification:

Dr. Tanya Kirilova Shivacheva has acquired specialties in Internal Medicine - 1989 and Rheumatology - 1997.

After acquiring a specialty in the healthcare system, Dr. T. Shivacheva continues her qualification with Ultrasound Diagnosis of the Musculoskeletal System, Good Clinical Practice, Pedagogical Competence, Interactive Teaching Methods, Research Methodology, as well as continuing medical education in Rheumatology, which certifies with the relevant certificates.

Experience

Dr. T. Shivacheva has extensive professional experience. She started working as a district therapist, continued as an intern in the Intensive Care Cardiology Department at the Cardiology Clinic. Since 1987 she has been working for over 30 years for the development and establishment of Rheumatology Science and Practice at the Medical University of Varna. She co-founded the Department of Rheumatology in 1987 and co-authored one of the first scientific reports focused on the diagnosis and treatment of Rheumatoid Arthritis. Masters and applies in daily clinical practice the peculiarities of the diagnosis and treatment of rheumatic diseases - intra-articular manipulations, imaging, ultrasound of the musculoskeletal system, participates in general hospital consultations and expert meetings at the national level. She is a member of the Commission for treatment with expensive drugs for patients with inflammatory joint diseases at the University Hospital "St. Marina EAD - Varna. Creates a register of patients with rheumatoid arthritis, treatment with biological molecules at DKB - rheumatology office at the University Hospital "St. Marina EAD - Varna.

Dr. T. Shivacheva is a member of the Bulgarian Medical Association, the Bulgarian Scientific Society of Rheumatology and the Bulgarian Medical Society of Osteoporosis and Osteoarthritis.

According to the professional qualification indicator, the candidate fulfills the requirements for acquiring the academic position "Associate Professor".

Research activity

In 2019, Dr. T. Shivacheva successfully defended a dissertation on "Study of clinical activity of patients with rheumatoid arthritis, treated with biological agents" and obtained an educational and scientific degree "Doctor".

To participate in this competition, Dr. T. Shivacheva presents **63 scientific papers**, **5 citations** in scientific journals, referenced and indexed in world-famous databases with scientific information and **9 reviews** in scientific journals, referenced and indexed in world-famous databases with scientific information.

A. ***Habilitation work (monograph) "The patient with rheumatoid arthritis - present and future", published by the Medical University of Varna, 2020, a total of 100 points;***

B. ***Publications:***

1. *To fulfil the minimum national requirements according by the Law from 2018 and the Rules of MU-Varna from 2019 - 7* ***full-text publications*** *in scientific journals, referenced or indexed by world-famous database (WOS or Scopus)* ***- a total of 212 points.***

2. *Outside the required minimum state requirements according by the Law from 2018 and the Rules of MU-Varna from 2019:*

    2.1. Full-text publications in scientific journals, referenced journals with scientific review referenced or indexed by world-famous database (WOS or Scopus) - 3 issues;

    2.2. Full-text publications in scientific journals, unreferenced and indexed in world-famous databases with scientific information - 4 issues;

    2.3. Participation in **national congresses**, symposia, conferences –30 numbers;

    2.4. Participation in **international congresses**, symposia, conferences - 17 numbers.

Dr. T. Shivacheva is **an individual author** of 5 of the presented scientific papers, co-authored -60, of which - **first** author - in 16, **second** author - in 13, **third** author - in 14, **subsequent** author - in 17 of the scientific papers.

C. Citation in scientific journals, referenced and indexed in world-famous databases with scientific information - 5 issues - 75 points

The indicated activity on this indicator exceeds the minimum state requirements of the Law and of the Regulations of the Medical University of Varna for acquiring the academic position of Associate Professor.

Scientific achievements and contributions

The scientific achievements and contributions of Dr. T. Shivacheva are the result of many years of research and have theoretical-methodological and practical-applied contributions. They can be divided into seven scientific fields:

1. Scientific field Rheumatoid arthritis

For the first time in our country, Dr. Shivacheva makes a *prognosis for 10-year survival* in patients with rheumatoid arthritis (RA) on treatment with expensive biological drugs. Through a single prognostic variable combining age and comorbidity, it shows a subsequent risk of death in this group of patients. The profile of a patient with RA, with treatment with biological molecules, with a poor prognosis (<30% probability of survival) in the next 10 years has been developed. Factors related to the nature of RA and its treatment that affect the prognostic 10-year survival of patients are analyzed. Key predictors related to the nature of the disease have been identified, which determine over 50% of the predicted 10-year survival. The importance of the amount of "residual" activity of RA (expressed by SDAI) in long-term treatment with biological drugs and the age at diagnosis for the predicted 10-year survival of patients is emphasized.

Dr. T. Shivacheva analyzes the *concomitant pathology* in RA patients on long-term treatment with biological drugs, its relationship with the residual activity of RA and their long-term prognosis. For this purpose, a register of patients has been created, which contains information about the underlying disease, concomitant pathology, assessment indices and treatment accompanying biological therapy. Diseases with a proven independent risk of adverse outcome in patients who passed the selection criteria before starting biological therapy were analyzed.

A relationship was found between the presence of some concomitant diseases and higher values of the index scores. It proves that index scores do not only reflect the "residual" activity of Rheumatoid Arthritis. The values of the indices are higher in the presence of concomitant diseases, representing an independent risk of earlier death.

A new field in rheumatology has been set. In her research, Dr. T. Shivacheva proves that the average activity of RA within a 12-month period of treatment with biological drugs above 3.2 for DAS28 (CRP) is a risk factor for the development of cardiovascular disease, and values of SDAIs above 11 are associated with a worse prognosis for survival in the next 10 years.

An optimized approach is proposed, taking into account the comorbidity of patients, which in the daily clinical practice in patients with rheumatoid arthritis, treatment with expensive target molecules will improve the cost-effectiveness of biological therapy and increase the benefits for patients.

Main emphasis in her scientific activity Dr. T. Shivacheva puts on cardiovascular diseases (CVD) in patients with RA. This is quite natural, due to the great "contribution" of these diseases to the long-term prognosis and life expectancy of patients. A higher proportion of CVD has been demonstrated among patients with inflammatory joint disease and a higher overall cardiovascular risk (2- and 10-year-old) compared to patients with osteoarthritis. A cardiovascular risk profile of RA patients, treated with biological drugs, in relation to traditional risk factors and those related to the nature of RA. In her dissertation and monograph, Dr. Shivacheva presents for the first time in Bulgaria cardiovascular risk characteristics (divided into traditional risk factors and factors related to RA and its treatment) in RA patients undergoing long-term treatment with biological disease-modifying target molecules. It proposes an algorithm to reduce the expected (predicted) cardiovascular morbidity in these patients. The algorithm solves some current issues related to increasing the life expectancy of patients with rheumatoid arthritis in the "biological" era.

Dr. T. Shivacheva is one of the pioneers who introduced in Bulgaria an index assessment of RA activity (Disease activity score 28) as a means of measuring the effectiveness of synthetic disease-modifying drugs. She then performed an in-depth analysis of the two variants of DAS28 (ESR and CRP) in measuring response to treatment to biological target molecules. Reported a significant disproportion between the estimates according to the two versions of DAS28 in categorizing the activity of RA with a generally accepted uniform scale. In his dissertation she

proposes an optimized scale of DAS 28 (CRP) in categorizing the activity of RA. Develops and approves a model for determining the trend of RA activity and defines an integrated assessment. It found that the expected cardiovascular morbidity in these patients depended on the average RA activity represented by DAS28 (CRP) using a generally accepted single scale for the two DAS28 variants.

Dr. T. Shivacheva deepens her research on different parts of DAS28 (ESR) - subjective (number of painful joints and VAS) and objective (number of swollen joints and laboratory indicator). The change in the values of DAS28 (ESR) during treatment with biological target molecules is due to a change in the objective indicators in the core of the index. The subjective part of the indicator-DAS28 (ESR) -P does not change significantly.

A significant volume of the papers submitted for review is related to the **established register of RA patients** who conduct long-term treatment with biological disease-modifying drugs. It provides an opportunity **to reveal significant patterns of biological therapy** in real clinical conditions in patients with RA:

- Delay in treatment compared to the diagnosis;
- Prolonged use of corticosteroids;
- Combination treatment with Methotrexate.

The influence of the "time" factor from diagnosis to "first dose" of a biological drug has been shown to be expressed in radiographic progression of RA and functional motor deficit. The relative share of patients with a real goal in treatment with biological drugs in daily clinical conditions and its retention for a 12-month period was established. Approximately one third of patients on biological therapy remain on monotherapy. The relative share of RA patients who do not adhere to the recommendations for combination therapy has been established, which is a common and constant problem in healthcare, especially for patients with chronic diseases. 38% of patients do not take Methotrexate. These data are the basis for optimizing daily rheumatological practice: talks, discussions, explaining the benefits of taking Methotrexate in the optimal dose, a shared solution for combination therapy.

Symptomatic therapy with corticosteroids (CS) in patients with RA on biological therapy is an important and significant focus of the scientific activity of Dr. T. Shivacheva. The conclusions from it are that the long-term intake of CS is associated with a more unfavorable cardiovascular risk profile and higher expected incidence of CVD compared to patients without CS in therapy.

In practice, this means compromising the benefits of biologic therapy and increasing costs. It is concluded that in-depth work is needed, both with doctors and patients, to explain the risk of this combination. The use of CS should be limited to the shortest possible period until the goal is achieved and then reduced and stopped.

Dr. Shivacheva has a significant contribution to the testing of new for Bulgaria synthetic (Leflunomide, Lobenzarit) and biological disease-modifying drugs (Tocilizumab, Adalimumab) in clinical rheumatology and practice, as well as in the introduction of apheresis methods in the complex treatment of RA. This is reflected in a series of scientific articles and reports in national and international rheumatology forums.

The candidate is a co-author of a number of scientific papers on new immunological markers of RA. The first in our country studies of antiperinuclear factor and antikeratin antibodies are presented. Their importance has been proven as immunological markers, the first members of a new family of anti-citrullinated protein antibodies in patients with RA. Today, they are defined as highly sensitive and specific serological markers of RA, providing an excellent alternative to the rheumatoid factor test in the diagnosis of RA.

2. **Scientific field Non-steroidal anti-inflammatory drugs**

A large part of the presented scientific activity is focused on non-steroidal anti-inflammatory drugs (NSAIDs). Feloran Retard, Aulin, Movalis, Arcoxia were tested sequentially. A good gastrointestinal safety profile has been demonstrated with selective COX-2 inhibitors. A more unfavorable cardiovascular risk profile was found in RA patients treated with NSAIDs compared to those without such NSAIDs. Thus, NSAIDs in patients treated with biologics may compromise their benefits.

3. **Scientific field Reactive arthritis:**

The candidate presents current for the study period publications and reports in the field of etiopathogenesis, clinical picture, therapeutic behavior and prognosis in patients with reactive arthritis. High sensitivity, specificity and relative diagnostic value of serum antibodies against Yersinia enterocolitica and Chlamydia trachomatis in patients with clinical evidence of reactive arthritis have been studied and established. Greater diagnostic value was found at higher antibody titers and in HLA-B27-positive patients with clinical manifestations of arthritis.

Studies on the treatment and prognosis of Reactive Arthritis analyzed a three-year prognosis depending on clinical features, timeliness and type of anti-inflammatory treatment, as well as antibody titer against Yersinia enterocolitica serotypes 03 and 09 and Chlamydia trachomatis. A favorable prognosis has been established with timely (early) initiation of treatment with an appropriate antibiotic or chemotherapeutic. The therapeutic efficacy of Ofloxacin and Sulfasalazine in these patients has been studied in vivo and in vitro, and significant improvement in clinical and laboratory signs of activity, reduction of antibody titer against Yersinia enterocolitica, Chlamydia antigen negative have been reported.

A prognostic model has been proposed in patients with reactive arthritis.

4. **Studies of new slow-acting, disease-modifying agents and chondroprotectors in inflammatory and degenerative joint diseases**

Dr. T. Shivacheva is a co-author of a number of scientific developments in the field of new slow-acting, disease-modifying drugs (Sulfasalazine) in patients with psoriatic arthritis and reactive arthritis, long-term antibiotic treatment (Ofloxacin) in patients with reactive arthritis and chondroprotectors (DONA) in patients with osteoarthritis.

5. **Studies in patients with osteoporosis**

The scientific achievements and contributions of the candidate in the field of Osteoporosis are in the study of the average duration of treatment, assessment of the degree of influence of concomitant pathological fracture on adherence and persistence in therapy, analysis of the main reasons for discontinuation of antiosteoporotic therapy.

In patients with rheumatoid arthritis, a pre-BMD Fracture Risk Assessment Tool (FRAX) score was studied to measure a 10-year risk of major osteoporotic fracture and hip fracture and compared with the BMD FRAX index. The clinical FRAX result has a high prognostic value for the need for treatment of osteoporosis.

The long-term efficacy of intravenous ibandronate in postmenopausal women has been studied. A significant increase in BMD was found over a 2-year follow-up period.

6. **Studies in autoimmune vascular diseases**

Dr. T. Shivacheva is a co-author of studies in patients with Systemic Lupus Erythematosus and Progressive Systemic Scleroderma (PSS) aimed at cardiovascular and CNS-related changes. A modified screening algorithm for pulmonary arterial hypertension based on the tricuspid gradient in patients with PSS has been proposed.

7. **Made up to date for the period (2003) analysis of rheumatological care in Northeastern Bulgaria.**

It is concluded that in Northeastern Bulgaria it is necessary to develop registers for basic nosological units, to introduce one-day hospitals in rheumatology, as well as to create opportunities for remote consultations. Today this is realized and leads to optimized rheumatological care in this part of the country.

Educational-teaching activity

Dr. T. Shivacheva began her teaching career in 1989 as an assistant in internal medicine, Clinic of Cardiology, Rheumatology with Intensive Care Cardiology, Higher Medical Institute - Varna and it is continuous until now. To date, she has over 30 years of teaching experience. She has successively held the positions of Senior Assistant and Chief Assistant, and since December 2020 she has been the Head of the Rheumatology Department at the First Department of Internal Medicine, Faculty of Medicine, MU-Varna.

In the last five years there is the following study load, which is reflected in the attached academic report:

Academic year 2014/2015 - 246 hours

Academic year 2015/2016 - 252 hours

Academic year 2016/2017 - 240 hours

Academic year 2017/2018 - 258 hours

Academic year 2018/2019 - 250 hours

Dr. T. Shivacheva applies a set of test combinations developed and implemented in the daily teaching activity for the exam in Internal Medicine of 4th year medical students. In the

conditions of an epidemic situation, she successfully applies distance forms of training and control of medical students in the Blackboard platform of MU-Varna, for which she has the relevant certificates.

In conclusion:

Dr. Tanya Kirilova Shivacheva is an established professional in the field of Internal Medicine and Rheumatology, with extensive knowledge and skills, excellent professional training and proven qualities. She has accumulated teaching experience and is respected by her students and colleagues. Her scientific output is sufficient in volume, exceeds the minimum state requirements and reflects her diverse interests as a researcher. Dr. Shivacheva covers all the requirements of the Law for the Development of the Academic Staff in the Republic of Bulgaria and the Regulations for the Development of the Academic Staff in MU-Varna for holding the academic position of "Associate Professor".

This gives me reason to strongly recommend to the respected members of the Scientific Jury to vote positively for the award of the academic position of "Associate Professor" to Dr. Tanya Kirilova Shivacheva.

18.07.2020 Prof. Dr. Sv. Georgiev, PhD

Varna