

RECENSION

on dissertation work under the procedure for obtaining a doctoral degree

Author of the dissertation: Dr. Tanya Kirilova Shivacheva,

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

Supervisor: Prof. Dr. Svetoslav Zhivkov Georgiev, PhD

Reviewer: Prof. Dr. Nikolai Yordanov Penkov, PhD, Executive Director of Specialized hospital for active treatment of Cardiology - Varna, Bulgarian Institute of Cardiology.

The thesis of Dr. Tanya Shivacheva examines a current problem in contemporary rheumatology - examines the clinical activity of rheumatoid arthritis, in patients undergoing treatment with biological agents and looking for the relationship with CVD and mortality. Rheumatoid arthritis is a chronic inflammatory and destructive arthropathy with a gradient course. It is known that over the last 20-25 years they have been accumulated a lot and compelling scientific data showing that atherosclerosis is an inflammatory disease. The starting point in this process is endothelial dysfunction. It is related to a number of factors and leads to reduce NO production and to the limit its beneficial effects - vasodilation, anti-inflammatory, antithrombotic action, etc. This process can be maintained and potentiated by the presence of a chronic inflammatory process such as RA. There have been reports in the past that patients with rheumatic disease who undergo active anti-inflammatory and antibiotic therapy have a lower incidence of Ischemic Heart Disease. In addition, it is considered proven that unstable forms of Ischemic Heart Disease in more than 50% of cases develop after intercurrent or any other infectious inflammatory disease. A study such as that of Dr. Shivacheva worth it admirations since the results from it could show whether there is a relationship and what is it between RA and CVD activity and mortality.

Thesis of Dr. Shivacheva as a result of a well-thought-out retrospective clinical trial and hides all the risks of this kind of research. The work is written on 190 standard pages and is illustrated with 62 figures and 33 tables.

The references are based on 292 titles, 2 of which are in Cyrillic and 290 in Latin, most of which have been published in the last 10 years. A historical review was made according to which the description of the classical picture of RA is from 1800, i.e. it is a relatively new disease for medical practice. The contemporary definition and social aspects of RA are discussed. It has been argued that RA leads to early mortality due to co-morbidities and persistent arthropathy activity. The strategies, goals and therapeutic behavior of RA patients are described in detail. A special place is separated of the evaluation of the activity of the disease process and the effectiveness of biological therapeutic agents. The quality of life of patients and its improvement in biological treatment were analyzed. The long-term prognosis is considered in two aspects - quality and life expectancy. A significant place is separated of concomitant RA diseases, as the accent is on CVD and mortality. The RA itself is not considered for lethal disease. Mortality in RA is due to extra-articular complications, most commonly infections and accompanying diseases, usually cardiovascular and neoplasms. Befitting place is given to traditional cardiovascular risk factors and an increasing role of the same from treatment with non-steroidal anti-inflammatory and corticosteroid drugs. The review shows that the author is well aware of the problem and analyzes the data extremely competently, as a result of which she concludes with conclusions that serve as a basis for the author's clinical study.

Purpose and the tasks of the study. The purpose of the dissertation is logically derived from unresolved and controversial issues and is defined accurately and clearly. Tasks, 5 in total, specify the paths for realization on the goal.

Clinical material and research methods used. The medical records of a total of 209 patients with RA were analyzed, passed through the diagnostic and consulting cabinet of the Clinic of Rheumatology, University Hospital "St. Marina" - Varna for the period from 01.06.2017 - 30.09.2018. After applying the selection criteria and the exclusion criteria for biological treatment, 197 patients remain. Two more patients were dropped - one due to a lung tumor and one due to acute multiple organ failure. 195 patients remain sufficient for the purpose of the study and meet the criteria of the National Health Insurance Fund for biological treatment. The methods for

examining patients are modern and highly informative, described in detail in the dissertation. They allow to obtain the information necessary to accomplish the purpose and the tasks set. The statistical analysis of the results is wide-ranging and uses methods that allow accurate assessment of their significance.

Results and discussion. Patients with RA treated with biological agents are usually women (85.3%), over 40 years of age (90.7%), with a disease duration over 10 years, with erosive joint changes in more than 65%, and with BMI is above normal at 66.5%. By increasing the duration and severity of RA, BMI is reduced and developed so-called rheumatoid “cachexia”. In 70.3% of patients with RA a concomitant disease is detected, in 61.3% of cases it is cardiovascular, with arterial hypotension in the first place and in the second place - Ischemic Heart Disease. The combination of RA with GCC is usually more common in the background on corticosteroid therapy, more painful joints, and higher VAS and DAS28 values. RA activity is presented with a higher average DAS 28 (ESR) than this on DAS 28 (CRP). The risk of increased CVD and mortality in RA patients with biologically active therapy is dependent on the activity of the disease process as determined by DAS 28 (CRP) values. Combining biological agents with synthetic agents - MTX reduces the risk, and combination with corticosteroids increases it. The predictive probability for CVD in RA patients can be significantly reduced by lowering the DAS 28 (CRP) limit. This is achieved by value of the indicator <2.67 , which categorizes patients as those with low RA activity. In the absence of a contraindication, it is essential to administer combination therapy with biological agents and MTX and to discontinue treatment with corticosteroids as soon as possible.

Conclusions. The purpose of the thesis is fulfilled. The conclusions are 6 in number. I think that they accurately, as well as clearly correspond to the tasks set and the results obtained.

Contributions to the thesis. Dr. Shivacheva's research is original and confirmatory. This is our first study, which he examines in the dynamics of RA activity, in the background on treatment with biological agents in different therapeutic models and depending on the accompanying CVD. Premature mortality in RA patients is discussed in detail and the reasons that cause it. The traditional risk factors for CVD in combination with the inflammatory process in RA and its treatment are analyzed. The activity of RA in patients with and without CVD was analyzed and presented with the two variants of the combined DAS28 indicator.

An indicator is offered clinical practice, representing the average activity of the RA over a time period. It gives a more realistic picture of RA activity during treatment, better prognostic information and avoids momentary effects on laboratory parameters. DAS28 (CRP) optimized values are proposed to more accurately assess residual RA activity and improve long-term prognosis of patients depending on CV risk. An algorithm for individual care in RA patients is proposed to improve prognosis: quality and life expectancy.

The abstract of the dissertation has a standard structure. Summarizes the dissertation accurately and clearly.

Publications and participation in scientific forums. Dr. Shivacheva presents 2 publications related to the dissertation. They are printed in reputable foreign scientific journals. It is noteworthy, however, that the publications precede the whole idea of dissertation work and the scientific research carried out after 5-6 years. This means linking publications to dissertation work is only thematic and they do not reflect the stages of the research.

CONCLUSION: Interesting scientific research addressing a current issue based on a sufficient number of retrospectively analyzed patients. The literary review is with scientific dignity and can serve as a reference for the topic, although it is loaded with lots of space propedeutical information. The purpose of the thesis and the tasks for its realization are formulated precisely and clearly. The clinical material is sufficient to accomplish the stated purpose and tasks. The research methods are modern and sufficiently informative. The results obtained are in line with the literature. They show the place and role of biological agents in the treatment of RA. The quality of life in RA patients is largely determined by the activity of arthropathy. Rheumatoid arthritis is not deadly disease. Its mortality is associated with infectious complications and accompanying CV and neoplastic diseases. The conclusions are 6 in number and exactly meet the set goal and tasks. The publications made in connection with the dissertation are 2 and do not reflect the work done in the scientific work. That is why I offer the author the data from the thesis to be further promoted among the cardiology and rheumatology communities in Bulgaria and abroad.

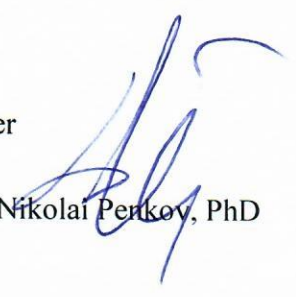
The scientific work of Dr. Shivacheva is a contribution and confirmatory nature and fully meets the requirements for the award of the educational and scientific degree "Doctor". That is why I suggest that the members of the jury vote on this with a positive vote.

September 28, 2019

Varna

Reviewer

Prof. Dr. Nikolai Perkov, PhD

A handwritten signature in blue ink, appearing to be 'N. Perkov', is written over the printed name of the reviewer.