



To the Scientific Jury
of Medical University - Plovdiv
under an award procedure
scientific and educational th degree "Doctor"
in the scientific field of Rheumatology

REVIEW

From **Assoc. Prof. Dr. Antoaneta Rangelova Bozukova -Toncheva, MD, PhD**,

Head of Department of Internal Medicine at National Multiprofile
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Regarding: for the defense of dissertation for awarding the educational and scientific degree "Doctor" in the doctoral program Rheumatology in a professional field - 7.1. Medicine in the field of higher education - 7. Health and sports in the scientific specialty - Rheumatology

Author of the dissertation : Dr. Krasimir Iliev Kraev

Subject : Study on the immunogenicity of TNF- α blocker drugs for the formation of drug-induced neutralizing antibodies in patients with inflammatory rheumatic joint diseases

Supervisor : Assoc . Dr. Mariela Geneva-Popova , MD, PhD

1. General presentation of the procedure and the doctoral student

Dr. Kraev presented all the documents in connection with his dissertation, which are required by MU-Plovdiv .

Dr. Krasimir Kraev was born in Plovdiv in 1989 . He graduated from English language school in 2008 and medicine in 2014.

From 2014 he was an assistant professor at the Department of Propedeutics of Internal Diseases at the Medical University of Plovdiv and PhD student on a self-study. From 2015 to 2019 he was a resident in rheumatology at the University Hospital "Kaspela" and in 2019 acquired specialty Rheumatology.

He has qualifications in capillaroscopy, in joint ultrasound - in Plovdiv and in Oxford and in nuclear-magnetic examination of axial spondylarthropathies in Munich. He has participated in numerous Bulgarian and international conferences and symposia with reports, posters and oral presentations. He was a researcher at 30 clinical trials for novel drugs in different rheumatic diseases.

2 . Relevance of the topic and expediency of the goals and objectives

Treatment with biological medicines is a qualitative leap in the therapy of the inflammatory autoimmune rheumatic diseases that changed the their course, the quality of life of patients and long-term outcomes. Biological treatment is also widely applied in a variety of other medical specialties. From 1998 to now the physicians gain experience of using these drugs and found that some patients do not have sufficient effect of treatment and do not achieve remission, others initially respond well, but then their therapeutical effect decreases and the condition worsens.

One of the possible causes according to many authors, is the formation of neutralizing antibodies in the serum of the patient during treatment with biological agents leading to the reduction or absence of the therapeutical effect.

This problem is extremely relevant, because on the one hand the treatment is compromised, and on the other hand - there is a big economic problem, because biological therapy is very expensive and is paid by the NHIF for 6 months ahead.

In its research Dr. Kraev aims to study the drug induced neutralizing antibodies in patients with RA, AS and PsA treated with TNF-alfa blockers, the connection of the antibodies with disease activity, the factors influencing their production and their predictive value for the effect of therapy.

To achieve this goal the disertant sets seven tasks which are formulated clearly and accurately and suggest multivariate examination of the scientific topics .

3 . Knowledge of the problem

From the thorough literary overview that is served very neatly, competently and intelligently it is apparent that Dr. Kraev knows in

details the scientific problem , both in Bulgaria and abroad and gives order to contribute to its future development

4 . Research methodology

To achieve the tasks Dr. Kraev has thoroughly examined his 213 patient for 4 years. The work on his dissertation lasted 5 years.

He used clinical, laboratory, instrumental , contemporary mathematical and statistical methods . Thus, an adequate answer to the tasks set for solving in the dissertation is obtained.

The team work in a number of healthcare institutions in Plovdiv and in Sofia under the control of the dissertation makes a very good impression .

5 . Characteristics and evaluation of the dissertation

Dr. Kraev presents his dissertation work of 219 pages, together with the appendices.

There is an introduction on 2 pages, the overview is placed on 48 pages, the scientific problem under consideration is presented clearly and competently enough. The brief characterization of the three studied inflammatory joint diseases is through the prism of the goal of the scientific development.

The purpose of the dissertation and the tasks are well formulated.

On 15 pages are presented in detail the treatment groups of patients, the control group, which are sufficient in number and the used methods as well.

The chapter " Results and discussion " covers 75 pages. The work is illustrated with 41 tables and 36 figures. I find it a good idea that each section ends with a discussion where the student focuses on the most important results and regularities. The chapter ends with Algorithm for monitoring patients with RA, AS and PsA for preventing the formation of drug-induced neutralizing antibodies to TNF-alfa blockers - adalimumab and etanercept, which would be of a benefit for the practice. At the 6th month level, in the presence of neutralizing antibodies, it is recommended to change the biological drug. I think it is appropriate to indicate the value of the antibodies above which this should be done. The same goes for the next steps in the algorithm.

In the chapter " Summary " of 15 pages , Dr. Kraev has done a thorough and competent analysis of the results obtained by him correctly compares them to the established so far by other scientists around the world and in our country .

The chapter "Conclusions and Contributions" follows. I was pleased to see that the conclusions and contributions were reworked mainly taking into account the remarks of the internal defense.

The seven conclusions in the dissertation synthesize the most important from the chapter "Results" . They are formulated clearly and precisely.

The dissertation is the first for Bulgaria on this topic and logically there are a number of contributions with original, scientifically applied and confirmatory character, which are formulated correctly.

The bibliography contains 369 current titles, 9 of them by Bulgarian authors.

The following is a chapter with a number of applications of informed consents, questionnaires , criteria , etc.

Remarks:

The study of antibodies against IL-6 goes on and is interpreted in parallel with that of antibodies against the TNF-alpha blocker without being aimed at the dissertation. However, it is mentioned in the set tasks. Given the importance of this mediator of inflammation I accept its inclusion in the dissertation as an enrichment.

There are some negligible technical errors in the dissertation, small repetitions, in some places the unit of measurement for adalimumab bioavailability has not been corrected.

FIG. 22 is for patients with RA, not for those with PsA, as written in the text, but this is not significant.

The great value of this modern and wonderfully done dissertation is on the one hand the problem of reducing the effect of biological treatment with TNF-alpha blockers in patients with autoimmune inflammatory rheumatic diseases due to the formation of drug-induced antibodies in the serum and on the other - the development and the presentation of a number of modern prognostic mathematical models for the occurrence of these antibodies by estimating scales, indices and risk factors.

6 . Evaluation of dissertation publications

Dr. Kraev has delivered a total of 14 scientific publications related to his work :

- three reviews - one in English
- six original articles - 4 in English, in 5 he is the first author
- four scientific papers - 2 in Bulgaria and 2 international, in which he is the first author
- a monograph on the topic of the dissertation in co-authorship with his supervisor "Drug-induced neutralizing antibodies against TNF-a blocker drugs"

The publications of Dr. Kraev far exceed requirements for scientific degree "doctor" .

My overall assessment of the thesis is very high. The work is structured properly, written competently, smart and modern. I believe in the great scientific and practical value of the results and prognostic mathematical models in this work.

CONCLUSION

The proposed dissertation is made carefully , competently and in intelligent; it meets the necessary requirements.

The material is sufficient, and is interpreted in depth. The results are valuable and will benefit so science and practice.

With great pleasure and confidence I give a positive vote and recommend to the honorable jury to award Dr. Krasimir Iliev Kraev educational and scientific degree "doctor" in a doctoral program in Rheumatology professional field - 7.1. Medicine in the field of higher education - 7. Health and sports in the scientific specialty - Rheumatology .

26.06.2020

Reviewer:
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