

REVIEW

A dissertation on the topic:

„Complex assessment of the efficacy of biologic therapy in patients with active ulcerative colitis “

For acquiring the educational and scientific degree "Doctor"

Scientific specialty "Gastroenterology"

professional field: Medicine

Author: Dr. Asiyana Hristoforova Petrova

Reviewer: Professor Dr. Ivaylo Petrov Vazharov, MD, Professor of Gastroenterology, Specialist in Internal Medicine and Gastroenterology, Head of MHAT – Varna, MMA

I. Defense procedure

By Order № P -109-385/ 25.08.2023 the Rector of the Medical University "Prof. Dr. Paraskev Stoyanov" – Varna on the basis of a decision of the Faculty Council of the Faculty of Medicine at the Medical University "Prof. Dr. Paraskev Stoyanov" – Varna according to Protocol № 8 / 21.08.2023 and report No 103-3895 / 24.08.2023 by Prof. Yoto Trifonov Yotov, MD – Dean of Faculty "Medicine" at Medical university Varna, I'm named to review the dissertation of Asiyana Hristoforova Petrova – physician – gastroenterologist at the Clinic of Gastroenterology at UMHAT " Sv. Marina" Varna on the topic: "Complex assessment of the efficacy of biologic therapy in patients with ulcerative colitis" for acquiring a scientific and scientific degree "Doctor" scientific specialty "Gastroenterology", professional field: Medicine.

My review is consistent with the requirements for preparing a review for acquiring the educational and scientific degree "Doctor".

II. Short biographical data

Dr. Asiyana Petrova was born in the town of Gabrovo on 17.02.1988. she graduated medicine at the Medical university "Prof. Dr. Paraskev Stoyanov" – Varna in 2013 with academic excellence. She acquired a specialty of Gastroenterology in 2021. She has certificates of professional qualification of abdominal ultrasound examination, upper and lower endoscopy – first and second level. Dr. Petrova works at the Clinic of Gastroenterology from 2016 and from 2019 she is assistant in Second

department of Internal diseases of MU – Varna. She is fluent in English and has a very good computer literacy.

I. Structure of the dissertation

The dissertation is 180 written pages: introduction 2 pages, literature overview 43 pages, objective and tasks 2 pages, material and methods used 6 pages, results 64 pages, conclusion 1 page, bibliography 229 literature sources, 17 of them in Cyrillic alphabet and 212 in Roman alphabet, appendix 26 pages, conclusions – 9, contribution – 9. The work is illustrated with 32 figures and 71 tables.

II. Actuality and significance of the dissertation

The dissertation is on a highly topical and significant subject – biologic therapy in patients with ulcerative colitis. Ulcerative colitis I chronic immune-mediated disease with high incidence in the developed countries and rapidly growing incidence in the highly industrialized countries. The pathogenesis of ulcerative colitis is complex and unclear yet. The diseases frequently progresses, proceeds with frequent attacks, therefore the clinical estimation and treatment should follow its dynamic nature. Ulcerative colitis occurs in relatively young people requiring a long term and continuous therapy allowing remission of the disease. The range and seriousness of the disease are leading considering the treatment of ulcerative colitis. The activity of the disease should be assessed objectively before starting the therapy. The purpose of the objective assessment is to define the relevance of the decision for therapy and direction for future estimation of the response to the therapy. There are multiple models for assessment of the seriousness of the ulcerative colitis, but the index of Mayo and Ulcerative Colitis Disease Activity Index (UCDAI) are the most widely used. During the last decades the conclusion was made that the best results are obtained in patients in which the mucosa was healed. Follow up of the inflammatory activity is important and the healing of the mucosa is considered as a appropriate end point in clinical studies, assessing the biological agents in patients with moderate to high activity of ulcerative colitis.

The dissertation is one of the first detail studies in the country regarding the patients with active ulcerative colitis under biologic therapy.

III. Literature overview

The literature overview is noteworthy with the detail etiology, pathogenesis of ulcerative colitis, its extraintestinal symptoms and the different indexes for assessment of the disease activity. All available biologic medicaments in our country are described, and the world practice is analyzed. The actual methods for diagnostics and follow up of the inflammatory activity of the patients with ulcerative colitis under biologic therapy.

The literature overview ends with a conclusion that obtaining a permanent remission is the main purpose in the contemporary biologic therapy.

The objective is clearly formulated – to perform a clinical assessment of the efficacy and safety profile of the biological therapy conducted in patients with active ulcerative colitis.

The relevant tasks are concrete and well defined for the allocated objective.

IV. Clinical material used in the dissertation.

Totally 107 patients with active form of ulcerative colitis are examined at the Clinic of gastroenterology for the period of 2015 – 01.08.2023. 52 women and 55 men were included, the average age of diagnosing 36.2+/- 14.3; minimal 12 years and maximal 71 years. Retrospective analysis of the medical documentation was performed for all of the examined patients. All patients filled a form for informed consent for participation in the clinical observation and questionnaires for the quality of life and fatigue estimation.

V. Methods

All the patients were examined according to the classic clinical requirements with the main diagnostic methods – anamnesis and physical examination. The anamnesis was taken in detail regarding the subjective complaints – number of defecations, with/without pathological admixtures, presence/absence of abdominal pain, febrility, extraintestinal symptoms, the concomitant disease, medicaments taken and harmful habits – smoking.

Clinical laboratory examinations as well as examination of fecal calprotectin are examined in all the included patients in the beginning and in the course of the study. Screening for opportunistic infections is performed for all 107 patients.

Therapeutic medical monitoring with examining the presence of anti-medicament antibodies and the concentration of the biologic agent in the blood by Elisa method is analyzed in 17 patients.

In all 107 patients abdominal ultrasound examination was performed, and analysis of the thickness of the large intestine wall in mm, presence/loss of

haustration, normal/absent peristalsis was performed. Whole fibrocolonoscopy was performed in all the examined patients before starting the biological treatment and every 12 months after that. Montreal classification is used for estimation of the range and seriousness of the ulcerative colitis in all patients.

In 85 patients the quality of life and degree of fatigue were estimated. Three questionnaires were used – Questionnaire for inflammatory intestinal diseases – IBDQ, Daily Fatigue Impact Scale – DFIS and Inflammatory bowel disease fatigue scale – IBD-F Scale.

VI. Results, algorithms of behavior, discussion, conclusions and contributions of the dissertation

The patients were analyzed according to the demographic indicators gender and age, concomitant diseases, extraintestinal symptoms. The first manifestation of the disease is most common between 25 and 65 years, but later manifestation is possible – after 65 years. The most common complaint before starting the biologic therapy is the abdominal pain in 102 (95.3%) patients, hematochezia – 106 (99.1%) and asteno-adyndamia in 76 (71%).

The results of the distribution of the patients were presented regarding the range of the disease according Montreal classification, the clinical symptoms, hematologic and biologic indicators, fecal markers. The average hemoglobin values in the patients included in the study during the period of observation have a tendency to increase and the favorable dynamics of this indicator demonstrates the control of the inflammatory process. A statistically significant relevance is described between the values of total protein and the seriousness of the disease. In the patients with values of albumin <3.5 g/l the diseases are more severe with more frequent necessary hospitalizations. Measuring the levels of CRP is an easy method of estimation of the activity and seriousness of the disease, and the data analysis included in this dissertation correspond to the ones reported by other authors. The positive dynamics during the treatment proves the importance of this indicator for estimation of the healing process. The greatest decrease of the average value in the examined group of patients between the compared periods is observed in the fecal calprotectin.

The place of ultrasound abdominal examination and fibrocolonoscopy in the diagnostics and follow up of the patients with ulcerative colitis is well described.

The distribution of the patients in groups according to the biologic medicament applied is visually presented, different correlations are noted regarding the main laboratory and imaging indicators. The most frequent adverse medicamentous events connected to the use of biologic agents are indicated.

A structured questionnaire is used for estimation of the quality of life, as well as two questionnaires assessing fatigue in patients with active form of ulcerative colitis undergoing biologic treatment.

The suggested algorithm for biologic therapy as well as creating of a functioning register at the Clinic of Gastroenterology is a significant contribution in the follow up of the patients with active form of ulcerative colitis.

The writer of the dissertation compares her own results to other authors' results.

The data are presented in detail in well-illustrated tables, figures and attachments.

The conclusions are 9, objectively reflecting the obtained results.

The most significant results of the study are summarized in the conclusion.

9 contributions are noted, having predominantly practical importance. A complex estimation of the patients with ulcerative colitis on biologic therapy is performed in Bulgaria for the first time.

The autoreferate is structured according to the requirements.

IX. Publications and scientific activity

2 publications are included in the dissertation of Dr. Petrova, related to the subject of the dissertation – as first author, and 3 scientific reports from international and national symposia and conferences.

X. Conclusion

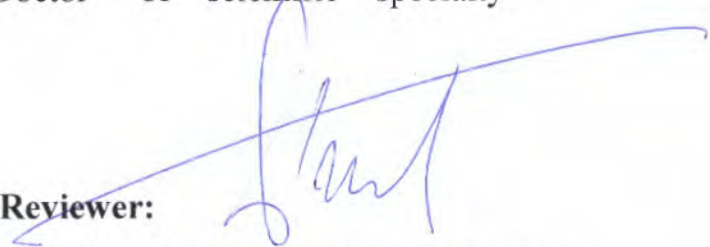
As a conclusion I think that the author of the dissertation demonstrated brilliant literary knowledge of the problem of biologic therapy in active form of ulcerative colitis as well as competent knowledge and qualification. The topic is actual and relevant for our country; the examination is well organized and conducted.

All that gives me the reason to express a high opinion of the scientific work and suggest to the scientific jury members at Medical University “ Prof. Dr. Paraskev Stoyanov” – Varna, to award Dr. Asiyana Hristoforova Petrova an educational and scientific degree “ Doctor” of scientific specialty “ Gastroenterology”.

14.10.2023

City of Varna

Reviewer:


Prof. Dr. Ivaylo Vazharov, MD