

## **STATEMENT ON PhD THESIS**

of D-r Asiana Hristoforova Petrova, entitled: „Complex assessment of the efficacy of biologic therapy in patients with active ulcerative colitis“ for obtaining the educational and scientific degree “PhD” – higher education field 7. “Healthcare and sport”, professional field 7.1 “Medicine”, scientific specialty 01.03.14. “Gastroenterology”.

**Scientific supervisor: Assoc. prof. D-r Diana Todorova Gancheva-Tomova, MD, PhD**

**Reviewer: Assoc. prof. Irina Ivanova Ivanova, MD, PhD;** Gastroenterologist and Internal medicine specialist, Head of Department of gastroenterology, University hospital “Sv. Marina”, Head of Second department of Internal diseases, Medical University “Dr Paraskev Stoyanov” - Varna

I have been entitled to present the current statement in accordance with a decision of the head of the Scientific jury and Medical University Rector’s order P-109-385/25.08.23 and Protocol N1/7.09.23.

### **1. Brief biographic and professional notes**

Dr. Asyana Petrova is a graduate of MU – Varna. Since graduation in 2013 she has been working at the Clinic of Gastroenterology at the University Hospital "St. Marina". In 2021, he acquired a specialty in Gastroenterology, with interests in lower GIT diseases and especially in diagnostics and follow-up of patients with inflammatory bowel diseases (IBD). In her training, she mastered the methods of abdominal ultrasound, upper and lower endoscopy. Dr. Petrova has been an assistant professor at the Department of Internal Diseases since 2019 and has been working for 4 years with medical students, trainee doctors and postgraduates in Gastroenterology. Dr. Asyana Petrova successfully finished her Ph.D. student education in the Second Department of Internal Diseases, as an independent form of training.

### **2. Relevance of the thesis’ topic**

Inflammatory bowel diseases (IBD) represent a severe and significant health problem due to the chronic progressive course, the involvement of young, professionally active people and the increasing incidence in industrialized countries. Treatment of moderately severe and severe forms of IBD is challenging, despite the "bouquet" of modern medications aimed at mediators and signalling pathways of inflammation. Necessary steps in patient care are: appropriate choice of drug approach; active monitoring of clinical response, dynamics in biomarkers, endoscopic and histological changes; change of therapy in cases where the goal is not achieved or there are side effects. The requirements for specialists conducting biological treatment of IBS go beyond the traditional for knowledge, competence, and experience, including a lot of work and dedication to work with patients. The analysis of the success and tolerability of the biological treatment of ulcerative colitis in a joint development for the clinical centre has not been conducted so far in Bulgaria.

### **3. Characteristics, volume, structure, and evaluation of the thesis**

The dissertation of Dr. Asyana Petrova consists of 180 pages and follows the traditional structure: introductory words - 2 pages; literature review – 43 pages; aim and main tasks – 1 page; patients and methods – 6 pages; results and discussion – 64 pages; final conclusions – 1 page; contributions – 1 page and literature reference from 229 sources, 17 of which by Bulgarian authors. The dissertation has a balanced content and is written in a clear, comprehensible, and comprehensive style.

The literature review is based on both the main and the most up-to-date publications, in consideration of the topic. Dr. Petrova makes a comprehensive and competent systematization for the disease Ulcerative colitis (UC) with the result of nice paper that is read pleasantly, can serve as a training, and is recommended for reading by prominent specialists in the field. The overview is illustrated by 2 tables and 7 figures.

The aim of the dissertation is clinically oriented: to assess the effectiveness and safety profile of biological therapy in patients with active UC. The tasks are seven - clearly stated to define the steps to proceed with the study. Patients' selection is according to the inclusion and exclusion criteria. Thus, the study involved 107 patients with a variation of age at diagnosis of UC from 12 to 71 years, who were treated with biological treatment for the period from its introduction to the therapeutic approach in 2015 until the completion of active surveillance for the purposes of the dissertation in 2023. The evolution of the disease is divided into two periods – primary, before starting biological therapy and during treatment. Patients are indicated and prepared for therapy according to the current "Criteria for initiating treatment of ulcerative colitis with biological medicinal products". An assessment of the IBD was conducted according to the Montreal classification of the range and severity of ulcerative colitis. Initially, and every 12 months of treatment, a complete colonoscopy was performed with follow-up of endoscopic Mayo score. The dynamics of generally accepted inflammatory biomarkers (CRP, faecal calprotectin) were analysed. In 85 patients, quality of life and degree of fatigue were examined by 3 questionnaires, 2 of which were specific to IBD. In 17 patients, data on therapeutic drug monitoring were collected.

Dr. Petrova makes an extensive clinical analysis of the age of patients at diagnosis, the initial spread and severity of UC, the frequency of smoking and concomitant diseases. When assessing the symptoms before starting biological therapy, in my opinion, the separation of "haematochezia" from "rectorrhagia" is unjustified because it is a degree difference in the same symptom. Dr. Petrova found that in women, extra-intestinal manifestations of UC were more common than in male sex (56% vs. 44%). The majority of the patients have pancolitis (67.3%), followed by left-sided colitis - 34 (31.8%) and proctitis - only 1 case. Biological therapy was started within 5 years of diagnosis of UC in 61.7% of cases. When comparing the main laboratory parameters initially and during follow-up during biological treatment, the dissertant showed a significant improvement in haemoglobin, a decrease in leukocyte and platelet count, an increase in the concentration of albumin in serum, a tendency to normalize serum iron and CRP. The most pronounced dynamics were reported in the faecal marker of inflammation, with an average calprotectin baseline of 1110.6 mg/kg, compared to 163 mg/kg at the end of the observation. The complex effect of therapy can be assessed by the abdominal ultrasonography, with evidence of reduction of the bowel thickness from a median



of 8 mm to 6 mm. The dissertation reports that monitoring the levels of the drug and the presence of antibodies to it is very useful in deciding to continue or change the therapeutic regimen. Analysis of the date of colonoscopy established: favourable dynamics in the indicator lack of haustration (46.7% vs. 9.3%); disappearance of mucosal erosions at 35.5%; reduction of the proportion of patients with ulcerative defects (from 98.1% to 40.2%) and contact bleeding (from 70.1% to 12.1%); only 50% of patients have a negative test for fragility of the vessels during observation. In general, the endoscopic activity decreased from 68% before starting biological treatment to 6.8%; 26.2% of patients achieve endoscopic remission. In 1/3 of the treated patients, the desired histological improvement, reported as mucosal healing is accomplished. The overall Mayo score decreased significantly from 11.7 to 3.8 over the course of the study. Interesting is analysis about the administration and outcome of steroid therapy. A major proportion of patients were treated with anti-TNF alfa agents: Adalimumab (52.3%); Infliximab and the biosimilar Inflectra (42.1%); Golimumab (5.7%). The experience of Vedolizumab administration was systematized in 27 patients and with Janus-kinase inhibitors (JAK) in 12 patients. "Switch" in biological therapy was required in 1/3 of the treated and a very important and detailed analysis of the reason for choosing another biological agent is provided. Increase in dosing, intensification of the regimen, is reported in 26% of cases. Azathioprine (35%) did not show a more beneficial effect on the overall Mayo score for the evaluation of therapeutic effectiveness. With each biological agent, the dissertation reported significant improvements in CRP, faecal calprotectin, and total Mayo score, which in dynamics pointed to a transition of patients into mild activity of UC. Beneficial response is reported in the quality of life of patients. The design of the study did not allow an academic comparison in the effectiveness and safety of different types of biological agents, but nevertheless the dissertation could use a graphical analysis of the comparative dynamics in the main markers of success (such as calprotectin, general and endoscopic Mayo score) to assess a small extent difference in baseline characteristics by subgroup and in response to biological agents. Dr. Petrova correctly notes the complexity of the therapy, including parenteral administration of human albumin, low molecular heparins, broad-spectrum antibiotics, oral vancomycin during flares of disease. Also, 64% of patients needed parenteral administration of iron supplement. Surgical treatment is reported in 1 patient. Side effects of therapy were systematically monitored. Dr. Petrova's observation is summarized in an electronic register of patients conducting biological therapy. The competent UC approach is summarized in an algorithm at the end of the "Results" section. The statistical methods correspond to the purpose and objectives of the survey and are competently indicated and used. The own results are excellently illustrated by more than 65 tables and 30 figures. A logical consequence of these results and discussion are 9 clearly formulated and informative conclusions. The bibliographic reference meets the requirements for completeness and timeliness. Dr. Petrova uses the published data from the leading researchers of IBD in Bulgaria.

Concerning the topic of the dissertation, Dr. Asyana Petrova provided 2 full-text publications and 3 participations in conferences with scientific reports, 1 of which is at an authoritative international forum. In all publications, Dr. Asyana Petrova is a leading author.

#### **4. Evaluation of the conclusions of the thesis**

I fully accept the stated conclusions and contributions of the dissertation.

## 5. Critical notes

No critical notes applicable.

## 6. Conclusion

The review of the dissertation work and proposed publications, as well as my impressions of Dr. Petrova's thorough and competent clinical work prove my positive opinion. I would like to recommend to the respected Scientific Jury to award Dr. Asiana Hristoforova Petrova the educational and scientific degree "Doctor" in the scientific specialty "Gastroenterology".

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Irina Ivanova  
MD, PhD



October 16, 2023,

Varna

/Assoc. Prof. Irina Ivanova, MD, PhD/