

REVIEW

by Prof. Dr. Iskren Kotzev, PhD, professor of internal medicine and gastroenterology

of the dissertation work on the topic "Complex evaluation of the effectiveness of biological therapy in patients with active ulcerative colitis" by Dr. Asiyana Hristophorova Petrova, assistant and physician at the Gastroenterology Clinic of UMBAL "St. Marina" at the Medical University, Varna, doctoral student in an independent form of study at the Department of "Internal Diseases", Education sector of Gastroenterology, Hepatology and Nutrition, Faculty of Medicine at the Medical University, Varna, for awarding the scientific and educational degree "doctor" in the field of higher education 7. healthcare and sports, professional direction 7.1. "Medicine", doctoral program "Gastroenterology"

By order, the R-109-385, Varna, from 25.08.2023 by Prof. Dr. Svetoslav Georgiev, MD - Rector of the Medical University, Varna, I was confirmed as a member of the scientific jury under the procedure for public defense of the dissertation of Dr. Asiyana Hristophorova Petrova on the topic "Complex evaluation of the effectiveness of biological therapy in patients with active ulcerative colitis". At the first meeting of the scientific jury on 12 September 2023. I was assigned to write a review. I have been provided with all the materials, which I have examined in detail and I confirm that the procedure for disclosure, development and admission to protection has been carried out in accordance with the requirements of the law on the development of the academic staff in the Republic of Bulgaria and the regulations for its application from 2010., as well as according to the requirements of the regulations for the development of the academic staff at the Medical University, Varna. I was guided by the same documents in the preparation of this review.

Even today, the treatment of life-long inflammatory bowel diseases (ulcerative colitis and Crohn's disease) remains a challenge to medicine, doctors and science. Along with the classical therapy with 5-ASA, glucocorticoids and immunosuppressants, in the 90s of the twentieth century, biological therapy entered in the therapeutic practice. With the help of recombinant technologies, the synthesized proteins act as antibodies against proinflammatory cytokines and block the expansion and self-maintenance of the chronic inflammatory process. The created blockers of TNF, antiinterleukins, antiintegrins revolutionized the treatment of chronic autoimmune inflammatory diseases in a short time and became the modern standard for the treatment of moderate and severe forms of IBD. Development of pharmacotherapy in the field of chronic self-sustaining autoimmune inflammatory diseases (incl. ulcerative colitis) continued with the discovery of small molecules - JAK-inhibitors, suppressing immune cell function - Tofacitinib и Upadacitinib, and sphingolipid modulators (Ozanimod, Etrasimod), regulating lymphocyte migration from lymph tissue to the site of inflammation.

In the course of treatment in patients with ulcerative colitis, there are many problems related to the choice of therapy, achieving and maintaining remission,

effectiveness of therapy, quantitative assessment of response, drug monitoring, and reduction .control of adverse drug effects, prevention of complications, nutrition, quality of life.

In her dissertation "Complex evaluation of the effectiveness of biological therapy in patients with active ulcerative colitis" Dr. Asiyana Hristophorova Petrova develops an extremely actual topic, which is currently a hot subject of numerous studies, disputes, with dynamically changing therapeutic consensus. In the last quarter century, inflammatory bowel diseases have been the subject of continuous and consistent innovations in the therapeutic approach. Scientific work is well motivated in scientific and practical terms. There are not many in-depth studies in our country and they are mainly in academic centers.

The Clinic where Dr. Petrova works has an indisputable merit (together with other Bulgarian University clinics) for the introduction in the clinical practice in Bulgaria of the biological treatment of patients with chronic idiopathic inflammatory bowel diseases. Dr. Petrova sets her ambitious goal to carry out a clinical assessment of the effectiveness and safety profile of the conducted biological therapy in patients with active ulcerative colitis. The chronic nature of ulcerative colitis and the risks associated with possible complications or aggressive treatment are extremely important in the approach to these patients. In order to achieve this goal, Dr. Petrova sets herself 7 main tasks, which in my opinion, she has performed perfectly. The most important tasks concern demography, the effectiveness of biological therapy in ulcerative colitis, undesirable side effects and quality of life. In addition, Dr. Petrova offers us a modern therapeutic algorithm for choosing a biological agent and predictors for a good response. Dr. Petrova also created a register of patients with biological therapy, which is an indisputable contribution to the care of these patients.

Dr. Petrova examined the indices of 107 patients with active ulcerative colitis, treated in the Gastroenterology clinic for 8 years, all of which were examined clinically, by laboratory, ultrasound, endoscopy and pathohistology. Strict criteria for inclusion in the study have been established, which have been met. The study of Dr. Petrova is a large and representative for Bulgaria study in this field, confirmed by clinical, laboratory, endoscopic, histological verification, using all modern possibilities for diagnosis and treatment.

The dissertation uses modern methods of research – clinical, laboratory, ultrasound, colonoscopy, pathohistology, classifying patients on the Montreal scale, Mayo index, modern quality of life questionnaire and fatigue index. .

The dissertation uses an adequate statistical apparatus, which perplex to draw valid statments and conclusions. The dissertation work is illustrated perfectly with 32 figures and 71 tables.

The scientific work is presented in 180 pages, structured in 9 chapters, the most important of which are: literary review, research methodology, results with discussion and conclusions. The ratio between the parts is correct, the language is clear and accurate, the author presents the complex matter in an accessible and understandable way. The bibliography presents virtually all contemporary publications related to the topic and consists of 229 author's publications (17 in Cyrillic and 212 in Latin).

The goals of ulcerative colitis therapy are: management of symptoms, induction of remission, biochemical remission, clinical remission, endoscopic remission, mucosal healing, histological remission, transmural remission, even molecular improvement, maintenance of remission and good quality of life. For the purpose of her dissertation, Dr. Petrova makes a longitudinal section in the dynamics of the disease in the studied contingent, taking into account in practice almost all these important goals using modern methodology.

In the chapter on her own results, she examined in detail the contingent with an average age of 36 years at the onset of the disease with an almost equal number of men and women, clinical form on Montreal classification, anthropometry, conducted treatment, clinical semiotics, extraintestinal manifestation, inflammatory biomarkers. Based on detailed studies and follow-up, the author found that early use of biological drugs or small molecules allows patients with active form of ulcerative colitis to achieve clinical, endoscopic and histological remission.

Dr. Petrova convincingly shows us that biologic agents show high efficacy and safety for induction and maintenance of remission in patients with moderate to severe forms of ulcerative colitis. Patients receive treatment with next biological agents: TNF-blockers - Infliximab, Adalimumab, Golimumab, antiintegrins - Vedolizumab and small molecules - Tofacitinib, Upadacitinib. The dynamics in hematological and biochemical indicators are studied in detail, which supports the thesis of earlier inclusion of biological therapy.

It is known that after the introduction of biological therapy in patients with ulcerative colitis there is a significant reduction in the need for radical surgical treatment. This is confirmed by Dr. Petrova's referral to surgical treatment of only one patient in the whole study cohort with applied biological treatment. Although the biological treatment performed varies widely (from 2 months to 8 years), the PhD student has enough patients with early onset of biological therapy under 5 years from the beginning (62%), which allows her to draw conclusions in favor of earlier therapy.

Dr. Petrova confirms categorically that the inflammatory biomarkers, including the fecal calprotectin, are useful, easily applicable and effective benchmarks for the follow-up of patients with active ulcerative colitis undergoing biological treatment.

Another well-researched and studied method by the dissertation is the ultrasound of the large intestine, which gives reason to recommend the method as a non-invasive diagnostic tool for assessing the activity in ulcerative colitis. It is shown in detail how the ultrasound signs observed before the start of treatment "thickened wall" and "disturbed hausturation" endure favorable dynamics after the inclusion of biological treatment. After treatment, Dr. Petrova recorded an ultrasound resolution of normal hausturation and the size of the thickened wall. Ultrasound changes can be used as a predictor of response to biological treatment.

Aggressive treatment in ulcerative colitis sometimes leads to reactivation of latent tuberculosis. The dissertation shows 6 cases with evidence of latent and active tuberculosis in which tuberculostatic therapy was conducted and after successful treatment in four of them biological therapy was resumed. The study correctly

presented two cases with exitus lethalis – 52 years and 55 years old with ulcerative pancolitis and causes pulmonary thromboembolism and complications of COVID – 19.

Ulcerative colitis was described in the study group as 26.2% with arthropathy, 3.7% with erythema nodosum, 2.8% with uveitis and 4.7% with primary sclerosing cholangitis. The most common extraintestinal manifestation is anemic syndrome – in 65.1% of the subjects studied.

Colonoscopy is central to the diagnosis, evaluation of coverage, and follow-up of patients with ulcerative colitis. The dissertation detailed the endoscopic picture with all the most important changes – extension, edema, haustration, erosions, ulcers, fragility of vessels, inflammatory polyposis, endoscopic Mayo-index. In the course of the study, the author reported mucosal healing in 33.6%. It confirms the importance of colonoscopy along with a comprehensive assessment of Mayo classification activity. Dr. Petrova points out the need for pathohistological monitoring in the course of biological treatment in order to accurately register mucosal healing.

Dr. Petrova describes a high efficacy of biological treatment in terms of inflammatory markers – a decrease in leukocyte count, CRP, ESR and FCP, as well as a significant increase in hemoglobin and serum iron indicators. Only 12.1% of the subjects experienced contact bleeding. This dynamic is determined by adequate and effective treatment with biological agents and small molecules. The data reported by the author are in line with those of leading European clinical centres.

Sideropenia associated with chronic inflammatory process and blood loss is known to occur in these patients. Dr. Petrova found that 70% of patients with ulcerative colitis needed intravenous iron, which treatment was conducted with good results. The place of classical ulcerative colitis therapy, as well as heparin, albumin and probiotics in the healing process is reported. Hypoalbuminaemia was detected in 16% with adequate therapy and in 24% with thrombophilia treated with low molecular weight heparin.

The most commonly used group of biological agents in the cohort under study is the TNF-blocker group (Adalimumab, Infliximab, Golimumab) - 73%, followed by antiintegrins (Vedolizumab) – 19% and small molecules (Tofacitinib and Upadacitinib) - 8%. In one third of the patients switches the biological agent in the course of the observation. In the case of primary and secondary resistance or unacceptable side effects of biologic therapy, switching is required. The dissertation included patients with 1 to 3 switches of biological therapy in the course of observation. 26.2% had an intensification of biological treatment. A comprehensive assessment of the outcome of the biological treatment is indicated by a follow-up of the overall Mayo index and a decrease of an average of 8 points, indicating an excellent effect.

Dr. Petrova created a register of patients with an active form of ulcerative colitis on biological treatment, containing detailed information about the patients' condition and the invasive studies carried out, The Register greatly facilitates the monitoring and making adequate decisions in these patients.

Dr. Petrova has developed an original algorithm for action. It suggests the

inclusion of biological treatment in the absence of a response to conventional therapy, in corticoid-dependent and corticoid-resistant patients. After a multifactorial analysis, the choice of a biological agent follows, and with a good response to treatment, the patient remains on a maintenance dose with the same agent. In the absence of a therapeutic response, reassessment and therapeutic drug monitoring followed by a therapeutic decision depending on the finding – intensification, addition of immunosuppressant or change of biological agent.

With her scientific work Dr. Asiana Petrova has original contributions:

- For the first time in Bulgaria, a comprehensive assessment of patients with active ulcerative colitis has been made on biological therapy in the course of the treatment.
- The importance of inflammatory markers in determining disease activity and tracking has been confirmed
- Ultrasound is assessed as a fast and reliable method for diagnosing active disease and tracking the effect of treatment
- Confirms the importance of colonoscopy, Mayo-index and pathohistology
- An original algorithm for biological treatment of patients with active ulcerative colitis has been proposed
- A register of patients with active form of ulcerative colitis and biological treatment has been established.

The contributions are scientifically applied and confirmatory and are directly applicable in clinical practice. With her thesis, Dr. Petrova confirms the high informative value of non-invasive methods for patient follow-up. The study and conclusions of Dr. Petrova are in line with the recommendations of the ECCO for a therapeutic approach in these patients.

Dr. Petrova has 2 publications in scientific journals where she is the first author and 3 scientific reports in national and international scientific conferences and symposia.

The following recommendations can be made:

- Given the in-depth research with original results, it is desirable that Dr. Petrova has a higher publishing activity
- To increase its scientific activity in national and international scientific forums with scientific messages, reports or posters
- To actively participate in the activities of the hospital IBD group
- It is good to use the European registry for patients with inflammatory bowel disease UR-CARE (subject to agreement by the hospital administration)
- We found no comment on mucosal dysplasia given the carcinogenic risk in UC
- A similar interest is the primary sclerosing cholangitis group, which deserves more detailed consideration
- Arthropathy subject to categorisation (peripheral and axial), treatment response not considered in this patient group
- We propose to study the correlation of fatigue index with sideremia (there are reports linking fatigue with sideremia)

The comments made do not reduce the value of the dissertation work. We allow

ourselves to do them for the future scientific and clinical development of the dissertante.

The results and conclusions achieved are a valuable contribution to Bulgarian gastroenterology. Dr. Asiyana Petrova is a young doctor with a growing reputation in the Scientific Society of Gastroenterology. She works in a leading clinic of Gastroenterology with head Assoc. Prof. Irina Ivanova, MD, with the expert participation of Assoc. Prof. Antonia Atanasova PhD, a leading expert in Bulgaria in the field of inflammatory bowel diseases, with the invaluable help of our early leaving Assoc. Prof. Miglena Stamboliyska, MD, and with the active assistance and guidance of Assoc. Prof. Diana Gancheva, MD, and in cooperation with all other colleagues from the clinic and the hospital.

Dr. Asiyana Petrova has graduated with excellent success her higher medical education in 2013., has a recognized specialty in gastroenterology since 2021. and nearly 10 years of medical experience. There are 2 testimonials of highly specialized activities in Gastroenterology in abdominal ultrasound with Doppler and therapeutic endoscopy – both with II level. She is an active participant in the therapeutic and scientific activity of the Clinic of Gastroenterology at the University Hospital in Varna, where she has been working since 2014., as well as in significant Bulgarian and international scientific forums on gastroenterology. He is a member of the National Society of Gastroenterology and the ECCO (for 2015).). She has participated in national and European congresses and symposia on gastroenterology and inflammatory bowel diseases in Barcellona, Prague and Bordeaux.

I have a long-term view on the development of Gastroenterology in Varna and in Bulgaria, I know Dr. Petrova as a conscientious researcher with an original handwriting, a respected and valuable clinical doctor, with extensive experience in the field of inflammatory bowel diseases.

The study of Dr. Asiyana Petrova is a thorough and scientific study with a comprehensive assessment of the effectiveness of biological therapy in patients with active ulcerative colitis. It has its remarkable scientific and practical contributions. I believe that this work has high scientific value and useful practical applicability.

Assessing the complete dissertation work of Dr. Petrova with its complex studies, impressive results, original contributions, scientific and practical significance, I believe that the presented dissertation work of Dr. Petrova fully meets the requirements for awarding the scientific and educational degree "Doctor" and I give my positive vote.

I recommend the same to the distinguished members of the scientific jury.

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