

REVIEW

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On the dissertation work "ANTIVIRAL THERAPY IN CHRONIC HEPATITIS B-DYNAMICS OF VIRAL MARKERS AND LONG-TERM RESULTS" by dr. Yoana Svetlozarova Stoyanova, full-time doctoral student in a full-time study in the doctoral program "Gastroenterology" at the Second Department of Internal Medicine, ES Gastroenterology, Hepatology and Nutrition, Faculty of Medicine at the Medical University of Varna "Prof. Dr Paraskev Stoyanov" with scientific supervisor Assoc. Prof. Dr. Irina Ivanova, PhD for obtaining the educational and scientific degree "Doctor" in the doctoral program "Gastroenterology", field of higher education 7. Healthcare and sports, professional direction 7.1 Medicine

The thesis submitted to me for official statement contains 106 pages and is illustrated with 47 figures and 15 tables. The cited literature includes 176 sources, of which 2 are in Cyrillic and 174 are in Latin.

The structure follows the usual way for dissertation development – introduction, literature review, aim and objectives, materials and methods, results, discussion, conclusions, references, publications and scientific contributions related to the dissertation. I believe that the ratio in the volume of individual sections is correct and corresponds to the tasks that each of them has. The dissertation is devoted to one of the most significant problems in clinical gastroenterology and hepatology. Chronic hepatitis B virus infection affects large cohorts of patients and is a major cause of chronic liver disease with an inflammatory process leading to the development of liver fibrosis and carcinogenesis. Treatment with nucleoside/nucleotide analogues is currently long-term. A very small percentage of patients achieve serologic recovery. This is an ongoing number of patients who regularly visit Gastroenterology and Hepatology clinics for evaluation and follow-up and no long-term evaluation of these patients has been conducted to date.

The literature review with its indisputable competence, awareness, relevance is one of the merits of the dissertation. The dissertation provides in-depth data and analyzes the different groups of patients evaluated, using virological, serological and biochemical markers together

with surrogate markers of fibrosis. The aim is clearly and precisely formulated. It logically follows from the data of the literature review - to make an up-to-date assessment of the effectiveness of antiviral treatment and the activity of chronic hepatitis B-virus infection in patients with long-term intake of nucleotide/nucleoside analogues. Various clinical, clinical-laboratory, immunological and instrumental methods are used. 84 patients treated with NUCs, in different stages of the disease, from hepatitis to cirrhosis, are followed up prospectively. A full range of instrumental, serological, biochemical and virological analyzes are performed to evaluate the results, including the level of HBcorAg, according to the scientific program.

The obtained results are well illustrated with tables and figures. To achieve the aim, dr. Stoyanova has set herself 8 tasks. Their implementation guarantees the obtaining of results allowing the fulfillment of the aim set. The dissertation presents a complete and comprehensive description of the role of chronic hepatitis B in the ongoing changes and monitoring of the different groups of patients. The evaluation of hepatitis B-virus infection treatment with nucleotide/nucleoside analogues in the long term is interesting- the high rate of virostatic effect (84.5%) is accompanied by a high biochemical response (91.6%), which is a very important factor for stopping fibrosis progression. Long-term intake over 10 years also gives a better serological response with a decrease in the quantitative HBsAg on average by 898 IU/ml or in 90% of patients. Also of interest are the HBcor associated proteins, where 67% of patients have between 3 and 4 log₁₀ IU/ml. The conclusion that even with a completely achieved serological clearance of HBsAg, the presence of HBcor Ag is found in the patients' serum is interesting. This is an important criterion as a risk factor for the occurrence of HCC and convincing evidence for the need for antiviral treatment in patients on immunosuppressive treatment, even with high anti-HBsAg. Long-term treatment results in reverse in fibrosis assessed by surrogate markers, ultrasound and elastography.

The discussion is competently done. The obtained results are thoroughly and objectively analyzed, comparing them with the literature data. Based on the results obtained and the studies carried out, 13 conclusions are drawn. The contributions are 4 and have original and confirmatory scientific-applied potential.

The bibliography includes a large number of modern scientific sources devoted to the problems that are the subject of the dissertation research. It is noteworthy that only 2 sources are cited in Cyrillic, 174 in Latin, and are related to original works devoted to HBV infection, assessment of fibrosis, biomarkers related to necroinflammatory activity and fibrosis, elastography, etc.

A list of 3 publications, with participation in national congresses, related to the topic of the dissertation with oral presentations as the first author, is presented.

The autoreferat fully reflects the content of the dissertation.

Dr. Yoana Stoyanova is a specialist in gastroenterology with over 5 years of clinical experience. She graduated from Medical University "Prof. Dr. Paraskev Stoyanov", Varna in 2018 with excellent marks and began her professional career at the Clinic of Internal Medicine at UMHAT "St. Marina", Varna. In 2019 she became an assistant lecturer at the Medical University of Varna and started teaching students from the Bulgarian and English program, and from January 2020 is a full-time doctoral student at the Second Department of Internal Medicine. In April 2022 she started working in the Gastroenterology clinic at UMHAT "St. Marina", and in December 2022 acquired a specialty in Gastroenterology. She speaks English, German and Italian.

In conclusion, the dissertation work is devoted to a clinical problem of great health, socio-economic and scientific importance. In it, Dr. Stoyanova competently studies essential aspects of the pathogenesis of liver damage in the presence of HBV infection, the course of the disease and evaluation of the treatment in a long-term aspect and the set goals and objectives are fulfilled. Interesting results of a theoretical and scientific-applied nature and contribution are achieved.

I believe that the dissertation "ANTIVIRAL THERAPY IN CHRONIC HEPATITIS B-DYNAMICS OF VIRAL MARKERS AND LONG-TERM RESULTS" by Dr. Yoana Svetlozarova Stoyanova meets the requirements for obtaining the educational and scientific degree "Doctor", medical and scientific specialty "Gastroenterology and I convincingly suggest the members of the scientific jury to vote positively.

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Statement prepared
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