

STATEMENT OF OPINION

By: Assoc. Prof. Dr. Milena Krasimirova Nikolova-Vlahova, MD, PhD

Regarding: Dissertation work for the acquisition of PhD ("Doctor") degree by Dr. Iskui Mnatsakan Erkanyan on the topic: "IgA NEPHROPATHY - CLINICAL, IMMUNOLOGICAL AND PATHOMORPHOLOGICAL CRITERIA FOR DIAGNOSIS AND THERAPEUTIC APPROACH"  
PhD Program in Nephrology

Scientific supervisors: Assoc. Prof. Dr. Eduard Tilkiyan, MD, PHD  
Prof. Dr. Iliyan Doikov, MD, PhD

This Opinion has been developed in accordance with the ZRASRB and the relevant Regulations for its application at MU-Plovdiv.

All submitted documents comply with the regulations of the Republic of Bulgaria.

*Brief biographical reference*

Dr. Iskui Erkanyan graduated from Plovdiv Medical University in 2010 with excellent marks. She obtained specialty in Nephrology (since 2015) and over 10 years specialty experience. She is a certified specialist for performing renal biopsy, a member of the Bulgarian physicians' union and Bulgarian society of nephrology. She has numerous publications in the field of nephrology and participation in national and international congresses in this scientific field. From 2018 she is a full-time assistant in Nephrology at the Medical University of Plovdiv. Her research interests are mainly, but not exclusively, in the field of immune nephropathies, echocardiographic methods and renal biopsy. She uses English for her preparation and studies.

*Actuality of the scientific work*

IgA glomerulonephritis is the most common immune nephropathy worldwide, without systemic and targeted treatment showing inexorable progression to terminal renal failure. Affected patients of both sexes, of all races, and the debut of the disease is most often at a young age, which is why the disease is gaining more and more social importance. The present dissertation is a systematic analysis of over 100 cases of biopsy-proven IgA nephropathy, in the framework of long-term and targeted studies, and evaluates the clinical, immunological and pathomorphological signs of the disease and their significance for the therapeutic outcome. Therefore, the topic of the dissertation work is especially relevant today, when we have more and more possibilities for diagnosis and treatment of this disease.

*Structure of the dissertation*

The presented dissertation is developed on 113 pages and is well illustrated with 10 tables, 35 figures, and 8 own microscopic photographs. It is structured correctly, compliance with generally accepted requirements. The literature reference is compiled from a total of 178 literary sources, both in Cyrillic and Latin, the majority of which are from the last 10 years. The literature review is presented on 31 pages and reviews the current knowledge of IgA nephropathy. The pathogenesis of primary IgA nephropathy and IgA-mediated renal damage in other diseases and conditions are reviewed in detail. Of particular interest is the part about the role of microRNA in the pathogenesis of IgA nephropathy. The pathological

features, diagnostic criteria and therapeutic options for the disease are presented, as well as the results of kidney transplantation.

Goals and objectives are clearly and precisely formulated. The aim of this dissertation work is "to study the clinical, immunological and pathomorphological criteria for diagnosis and differential diagnosis of patients with IgA nephropathy and their importance for the therapeutic approach." To achieve this goal, Dr. Erkanyan sets the following tasks:

1. To evaluate the prevalence of patients with IgAN in whom the diagnosis is confirmed with renal biopsy.
2. To specify the prevalence of secondary IgAN.
3. To evaluate the use of other biomarkers in the diagnosis and therapeutic approach of IgAN.
4. To study the diagnostic value of serum and tissue IL-6 levels, as well as the difference in primary and secondary IL-6.
5. To study the relationship of pathomorphological changes with clinical presentation.
6. To explore the role of immunological studies in diagnosis, follow-up of activity and therapy.
7. To follow the clinical course of IgAN in different age groups.
8. To give recommendations for therapeutic behavior in patients depending on the clinical presentation, immunological and pathomorphological changes.

The study included 110 patients, 84 men and 26 women, with biopsy-proven IgA nephropathy, treated at the Nephrology Clinic at the University Hospital Kaspela for a period of 13 years. (2010-2023). In all patients, according to a standard US-assisted method, a renal biopsy was performed, clinical and laboratory tests of blood and urine, immunological tests (autoantibodies and C3+C4 fractions of complement) were performed, glomerular filtration was calculated, interleukin 6 levels were examined. The obtained data were analyzed using modern statistical methods using standard statistical packages.

The results are presented clearly and well illustrated with tables and graphs. The combination of IgA nephropathy with immune arthropathies, psoriasis, hepatitis B is of interest. The biopsy finding is illustrated with own histological images, incl. by immunofluorescence and conventional light microscopy.

A novel element of the study was the assessment of interleukin 6 levels, which were shown to be higher in women and to correlate with more pronounced tubulo-interstitial inflammatory infiltrates.

Dr. Erkanyan also presents the main therapeutic strategies for patients with IgA nephritis:

1. Therapy with only RAAS inhibitor is available in 11 patients, all of them have a proteinuria level below 500 mg/24h; 1 on HD
2. Methylprednisolone - pulse therapy was carried out in 82 patients
3. Cyclophosphamide - 54
4. MMF – 11
5. Azathioprine – 10
6. Advagraph – 1
7. Budesonide – 24, of them only 1 as initiating therapy
8. 17 patients received dapagliflozin.

For the first time in Bulgaria, the doctoral student describes systemic treatment of staining with Budesonide - in a total of 24 patients. Treated for a period between 3 and 20 months with good tolerance.

Dr. Erkanyan also evaluates the effect of the gluten-free diet in the studied patients and reports a good effect on the clinical and laboratory signs in the followed patients, emphasizing that at the start of this dietary regimen, the patients were without reversible proteinuria, nitrogen retention or systemic manifestations . These data raise the question of the importance of a gluten-free diet as an additional means of influencing mild forms of IgA nephritis.

The discussion is presented on 6 pages and clearly emphasizes the significance of the obtained results against the background of data in the literature to date.

There are a total of 8 conclusions and they fully meet the set tasks:

1. The conducted research confirms the data that IgAN is the most common glomerulopathy in patients up to 60 years old. age with male predominance.
2. The results show a similar profile of light microscopic diagnoses to those in most large studies, but also some differences in the immunofluorescence study - a low percentage of IgG and C4 deposition.
3. Elevated levels of serum IgA were demonstrated only in 2 patients and cannot be a diagnostic criterion.
4. The study of IL-6 showed significantly higher serum levels among patients compared to healthy controls. Comparison with histological changes showed that patients with higher levels of IL-6 demonstrated more pronounced levels of interstitial infiltrates, mesangial hypercellularity, as well as higher levels of fibrosis compared to patients with lower levels.
5. The effect of the ongoing treatment shows very good results in patients with medium and high risk, especially with early diagnosis and initiation of therapy.
6. In the patients treated with Budesonide, the data from the studies carried out so far for a good effect on the kidney function are confirmed. None had proven IBD and no positive antigliadin antibodies were detected.
7. It is confirmed that the leading renal pathology in Ps/PsA is IgAN
8. Therapy for IgAN should be specified according to the leading immune cause, respectively primary or secondary.

The dissertation presents a total of 5 contributions, of which perhaps the evaluation of the levels of interleukin 6 and their relationship with the activity markers of IgA nephritis and the presented therapeutic experience with budesonide are worth mentioning. An algorithm was created for the early diagnosis of IgA nephritis and the therapeutic options depending on the histopathological finding and accompanying/underlying staining and conditions.

The bibliography includes over 170 sources, both in Bulgarian and in English, most of which are from the last 10 years.

Dr. Erkanyan presents three publications in connection with the dissertation work, incl. in journals indexed in Scopus, as well as two contributions in scientific forms, the abstract of one of which was published in a supplement to the most respected journal in the field of nephrology - Nephrology, dialysis and transplantation.

The dissertation is written in good Bulgarian language, without unnecessary borrowings and foreign words, and is illustrated with a sufficient number of tables and figures. The several technical errors in the text by no means undermine the significance of the work.

The abstract is written in the good Bulgarian language and complies with all requirements.

*Personal impressions*


I have known Dr. Erkanyan for more than 10 years, and several times I have had the pleasure to be present at her presentations on Bulgarian scientific forums. In every contact with her, I was impressed by her determination and desire to find a logical explanation for every question or finding.

*In conclusion*, the dissertation presented by Dr. Erkanyan is in a finished form and demonstrates the results of the follow-up and treatment of a sufficient number of patients with IgA nephropathy at one university center. It was developed on the basis of sufficient clinical and histological material, the data were analyzed with modern statistical methods and presented clearly, incl. illustrated with graphs and tables and own photographic material from histological examination of kidney biopsies. The conclusions of the dissertation fully correspond to the set goal and tasks of the study. The dissertation has undoubted scientific and practical contributions and three publications are based on its data, incl. in Scopus indexed journals. The dissertation meets all the requirements of the regulatory acts of the Republic of Bulgaria for the obtaining of the PhD degree ("Doctor"). Everything so far gives me the reason to vote "FOR" the awarding the PhD degree ("Doctor") to Dr. Iskui Erkanyan. I would like to recommend to the other members of the honorable jury to give a positive vote.

November, 2024  
Sofia

Sincerely:

Assoc. Prof. Dr. Milena Krasimirova Nikolova-Vlahova, MD, PhD



Заличено на основание  
Чл.5 §1, 6."В" Регламент (ЕС)2016/679

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