Clinical Characteristics of Immunoglobulin M Deposition in Patients with Primary IgA Nephropathy

Feng Shaoqiang

Jinzhou Medical University, China

Abstract: IgA nephropathy is a complex renal disease characterized by the deposition of IgA immune complexes within the glomeruli. This article provides a comprehensive analysis of the pathological classification, clinical features, diagnosis, and treatment advances in IgA nephropathy. The Oxford classification system offers a standardized approach to the pathological classification of IgA nephropathy and serves as a reference for prognostic assessment. Additionally, patients with IgA nephropathy accompanied by IgM deposition exhibit specific clinical manifestations, such as hematuria, proteinuria, and hypertension. Further research should focus on elucidating the pathogenesis of the disease, identifying biomarkers, developing individualized treatment strategies, and investigating long-term prognosis and epidemiological characteristics. This review provides a comprehensive understanding of IgA nephropathy to guide its diagnosis and treatment.

Keywords: IgA nephropathy; IgM deposition; pathological classification; Oxford classification; clinical features; diagnosis; treatment; prognosis; biomarkers; individualized treatment; epidemiological characteristics

Primary IgA nephropathy is the most common primary glomerulonephritis worldwide, characterized by the deposition of immunoglobulin A (IgA) in the glomerular mesangium. It is a complex and heterogeneous renal disorder with variable clinical manifestations and outcomes. While the predominant deposition of IgA is the hallmark of the disease, recent studies have highlighted the clinical significance of immunoglobulin M (IgM) deposition in patients with primary IgA nephropathy.

The aim of this study is to investigate the clinical characteristics of IgM deposition in patients with primary IgA nephropathy. Understanding the role of IgM deposition in the pathogenesis and progression of this disease may contribute to the development of novel therapeutic strategies and prognostic markers.

In this study, we will examine the clinical features associated with IgM deposition in primary IgA nephropathy patients, including the relationship between IgM deposition and disease progression, as well as its potential correlation with prognosis. Additionally, we will explore the diagnostic and differential diagnostic approaches for identifying IgM deposition in primary IgA nephropathy.

By elucidating the clinical significance and implications of IgM deposition in primary IgA nephropathy, our findings may provide valuable insights into the pathogenesis, diagnosis, and management of this complex renal disorder.

1 Overview of Immunoglobulin A (IgA) Nephropathy

1.1 Definition and Classification

Immunoglobulin A (IgA) nephropathy, also known as Berger's disease, is a chronic kidney disease characterized by the deposition of IgA in the glomerular mesangium. It is the most common form of primary glomerulonephritis worldwide.

The classification of IgA nephropathy is based on the predominant histological features observed on renal biopsy. The Oxford classification is widely used and includes four main histological lesions: mesangial hypercellularity, endocapillary hypercellularity, segmental glomerulosclerosis, and tubular atrophy/interstitial fibrosis. This classification system provides valuable prognostic information and helps guide treatment decisions.

1.2 Pathogenesis

The exact pathogenesis of IgA nephropathy is still not fully understood. It is believed to involve a combination of genetic predisposition, aberrant mucosal immune response, and environmental triggers. It is thought that abnormalities in the glycosylation of the IgA molecule lead to the formation of immune complexes, which deposit in the glomerular mesangium and activate inflammatory pathways. This immune complex deposition and subsequent inflammation contribute to the development and progression of renal injury.

1.3 Epidemiological Characteristics

IgA nephropathy is a globally distributed disease, but its prevalence varies among different ethnic groups and geographical regions. It is more common in Asian populations, particularly in East Asia, compared to Western populations. The disease can affect individuals of all ages, but it most commonly presents in young adults. There is a male predominance in some populations, while in others, the male-to-female ratio is nearly equal.

Certain risk factors, such as respiratory or gastrointestinal infections, may trigger the onset or exacerbation of IgA nephropathy. It has also been associated with other systemic diseases, such as liver cirrhosis and celiac disease. Understanding the epidemiological characteristics of IgA nephropathy is important for identifying high-risk populations and implementing appropriate prevention and management strategies.

Overall, gaining a comprehensive understanding of the overview, classification, pathogenesis, and epidemiology of IgA nephropathy is crucial for effective diagnosis, treatment, and

management of this prevalent kidney disease.

2 Deposition of Immunoglobulin M (IgM) in IgA Nephropathy

2.1 Clinical and Pathological Features of IgM Deposition

In addition to Immunoglobulin A (IgA) deposition, IgM deposition is commonly observed in IgA nephropathy. The presence of IgM in the glomerular mesangium is associated with distinct clinical and pathological characteristics. On renal biopsy, IgM deposits are typically seen as granular staining in the mesangial area, often co-localized with IgA deposits.

The clinical significance of IgM deposition in IgA nephropathy is still a subject of debate. Some studies have suggested that the extent of IgM deposition correlates with disease severity and predicts a higher risk of progression to end-stage renal disease. Patients with increased IgM deposition tend to have more severe symptoms, such as persistent proteinuria and hypertension. Additionally, IgM deposition has been associated with more extensive glomerular and tubulointerstitial damage on histological examination.

2.2 Relationship between IgM Deposition and Disease Progression

The exact relationship between IgM deposition and disease progression in IgA nephropathy is complex and not fully understood. Various studies have investigated this association, but conflicting findings have been reported.

One proposed mechanism for the relationship between IgM deposition and disease progression is the activation of the complement system. It has been suggested that IgM immune complexes, when deposited in the glomerular mesangium, can activate the alternative complement pathway. This can lead to the recruitment and activation of inflammatory cells, such as neutrophils and macrophages, causing local inflammation and tissue damage. The ongoing inflammation and immune response can then contribute to the progression of renal injury.

In support of this hypothesis, several studies have demonstrated that increased IgM deposition is associated with more severe glomerular and tubulointerstitial damage, as evidenced by histopathological findings. These studies have reported a higher prevalence of glomerulosclerosis, crescent formation, interstitial fibrosis, and tubular atrophy in patients with increased IgM deposition. These pathological changes are indicators of more advanced disease and are associated with a worse prognosis.

Moreover, some evidence suggests that the presence of IgM deposition is associated with a higher risk of proteinuria persistence and hypertension, both of which are risk factors for disease progression. IgM deposition has been found to be more common in patients with persistent proteinuria, and the severity of proteinuria has been positively correlated with the degree of IgM deposition.

On the other hand, some studies have reported conflicting results regarding the relationship between IgM deposition and disease progression. These studies have found no significant association between the extent of IgM deposition and renal outcomes, including the rate of decline in renal function or the development of end-stage renal disease. Some of these studies even suggest that IgM deposition may be a relatively benign phenomenon in IgA nephropathy, having no independent impact on disease progression.

The conflicting findings may be attributed to several factors, including differences in patient populations, variability in study design, and the complexity of IgA nephropathy as a disease entity. The heterogeneity of the disease, with variations in clinical presentation, histopathological features, and underlying immune mechanisms, may contribute to the discrepant findings.

Further research is necessary to better understand the relationship between IgM deposition and disease progression in IgA nephropathy. This includes large-scale prospective studies, ideally with standardized methodologies for assessing IgM deposition and well-defined clinical and histopathological parameters. Clarifying the underlying mechanisms and identifying potential therapeutic targets related to IgM deposition could significantly improve the management and prognosis of patients with IgA nephropathy.

2.3 Correlation between IgM Deposition and Prognosis

The prognostic significance of IgM deposition in IgA nephropathy has been a topic of investigation in numerous studies. The presence and extent of IgM deposition have been proposed as potential markers of disease severity and poor prognosis. However, the consensus on the prognostic value of IgM deposition remains elusive due to conflicting findings from different studies.

Several studies have reported that increased IgM deposition is associated with worse renal outcomes in IgA nephropathy. Patients with higher levels of IgM deposits tend to have a higher risk of disease progression to end-stage renal disease (ESRD). They may also experience a more rapid decline in kidney function over time compared to those with minimal IgM deposition.

Moreover, IgM deposition has been linked to the presence of more severe renal lesions, such as glomerulosclerosis, interstitial fibrosis, and tubular atrophy, which are indicators of progressive kidney damage. These pathological changes are associated with an unfavorable prognosis and an increased likelihood of experiencing renal-related complications.

In addition to the histological features, the presence of IgM deposition has been correlated with clinical manifestations that signify a poorer prognosis. Patients with increased IgM deposition are more likely to exhibit persistent proteinuria, a common finding in advanced stages of IgA nephropathy. Persistent proteinuria is associated with an increased risk of kidney function deterioration and kidney-related events.

However, it is important to note that conflicting evidence exists regarding the prognostic significance of IgM deposition. Some studies have reported no significant association between IgM deposition and long-term renal outcomes, such as the rate of kidney function decline or the development of ESRD. These studies suggest that IgM deposition may be a less relevant prognostic factor compared to other clinical factors, such as baseline proteinuria levels, blood pressure control, and renal function at presentation.

The conflicting results may be attributed to the inherent complexities of IgA nephropathy as a disease entity. IgA nephropathy exhibits substantial heterogeneity in terms of its clinical presentation, disease progression, and underlying immune mechanisms. This heterogeneity may contribute to the variable prognostic implications of IgM deposition observed across different studies.

Further research is warranted to elucidate the precise

prognostic value of IgM deposition in IgA nephropathy. Large-scale prospective studies, incorporating standardized methodologies for assessing IgM deposition and rigorous follow-up protocols, are needed to provide more definitive conclusions. Additionally, comprehensive assessments of other clinical and histopathological parameters, along with genetic and molecular profiling, may help refine the prognostic stratification and guide personalized management strategies in IgA nephropathy.

3 Clinical Features and Presentations

3.1 Clinical Features of Hematuria and Proteinuria

Hematuria and proteinuria are characteristic clinical features of IgA nephropathy. They play a crucial role in the diagnosis, assessment of disease severity, and monitoring of disease progression. Here, we discuss the clinical characteristics and presentation of hematuria and proteinuria in IgA nephropathy.

Microscopic Hematuria: Microscopic hematuria, defined as the presence of red blood cells in the urine that are not visible to the naked eye, is the most common presentation of hematuria in IgA nephropathy. It is typically persistent and often mild, with occasional episodes of macroscopic hematuria.

Macroscopic Hematuria: Macroscopic or gross hematuria, characterized by visible blood in the urine, frequently occurs after upper respiratory tract infections or exercise. These episodes tend to be self-limiting and resolve within days.

Variable Proteinuria: The degree of proteinuria in IgA nephropathy can vary widely, ranging from mild to nephrotic-range proteinuria. Proteinuria is usually non-selective and consists of both albumin and low-molecular-weight proteins.

Persistent Proteinuria: Persistent proteinuria is common in IgA nephropathy and is associated with worse prognosis. It may occur concurrently with hematuria or manifest independently.

To better illustrate the clinical features of hematuria and proteinuria in IgA nephropathy, the following table provides an overview of the prevalence and characteristics of these manifestations in different studies:

Study	Hematuria Prevalence	Proteinuria Prevalence	Hematuria Characteristics	Proteinuria Characteristics
Shimizu et al. (2011) [1]	100%	91.3%	Microscopic; Occasional macroscopic	Mild to nephrotic-range; Non-selective
D'Amico et al. (2000) [2]	Not specified	75%	Not specified	Not specified
Katafuchi et al. (1993) [3]	100%	72.1%	Microscopic; Occasional macroscopic	Mild to moderate; Non-selective
Manno et al. (2017) [4]	96.4%	74.4%	Not specified	Not specified
Li et al. (2019) [5]	94.3%	57.3%	Microscopic; Occasional macroscopic	Mild to moderate; Non-selective
Xie et al. (2014) [6]	92.9%	62.4%	Microscopic; Occasional macroscopic	Mild to moderate; Non-selective
Maillard et al. (2005) [7]	92%	70%	Occasional macroscopic	Mild to moderate; Non-selective

3.2 Manifestations of Renal Dysfunction

In addition to hematuria and proteinuria, IgA nephropathy can be associated with various manifestations of renal dysfunction. These may include:

Elevated Blood Pressure: Hypertension is a common finding in IgA nephropathy, especially in advanced stages of the disease. It can contribute to the progression of renal damage and is associated with an increased risk of cardiovascular complications.

Decreased Glomerular Filtration Rate (GFR): Progressive decline in kidney function is a significant concern in IgA nephropathy. Decreased GFR is an indicator of impaired renal function and can be assessed using estimated GFR (eGFR) calculation methods, such as the Modification of Diet in Renal Disease (MDRD) formula or the Chronic Kidney Disease Epidemiology Collaboration (CKD-EPI) equation.

3.3 Other Relevant Clinical Presentations

While hematuria, proteinuria, and renal dysfunction are the primary clinical features of IgA nephropathy, there are several other clinical manifestations that are worth mentioning:

Hemoptysis: In rare cases, hemoptysis (coughing up blood) may occur due to the deposition of IgA immune complexes in the lungs. This manifestation typically follows episodes of macroscopic hematuria and is associated with more severe renal disease.

Abdominal Pain: Some individuals with IgA nephropathy may experience abdominal pain, which can be associated with renal or gastrointestinal involvement. It is important to consider other possible causes of abdominal pain and determine the appropriate management.

Edema: Edema, particularly peripheral edema of the lower extremities, may be present in patients with significant proteinuria and nephrotic syndrome. Edema results from the leakage of proteins, including albumin, from the blood vessels into the surrounding tissues.

It is essential to note that the clinical manifestations of IgA nephropathy can vary among individuals, and not all patients will exhibit all of the mentioned features. Additionally, the severity of these manifestations can differ among patients and may change over the course of the disease.

4 Diagnosis and Differential Diagnosis

4.1 Urine Examination

A urine examination plays a vital role in the diagnosis of IgA nephropathy and helps differentiate it from other kidney diseases. The following parameters are typically evaluated during a urine examination:

Hematuria:

Microscopic Examination. Microscopic examination of urine sediment reveals the presence of red blood cells (RBCs). Microscopic hematuria is a hallmark of IgA nephropathy. It is defined as the presence of greater than 5 red blood cells per high-power field (HPF) in at least three out of three freshly collected specimens.

Proteinuria:

Dipstick Test. Proteinuria is detected using a dipstick test, which provides a semi-quantitative measure of protein levels in the urine. The presence of proteinuria suggests the involvement of glomerular structures and is a characteristic finding in IgA nephropathy.

Urine Protein-to-Creatinine Ratio (PCR). A more accurate quantitative assessment of proteinuria is obtained by measuring the protein-to-creatinine ratio in a spot urine sample. A PCR value >0.5 g/g indicates significant proteinuria.

Other Urine Parameters:

Glomerular Hematuria. Immunofluorescence microscopy or phase contrast microscopy can help differentiate glomerular hematuria from non-glomerular causes. The presence of dysmorphic red blood cells, red cell casts, or subnephrotic-range proteinuria may indicate glomerular involvement.

4.2 Renal Biopsy

Renal biopsy is the gold standard for diagnosing IgA nephropathy and evaluating its severity. It provides important information about the histopathological features of the kidney and helps guide treatment decisions. The following histological findings are typically observed in IgA nephropathy:

Mesangial Proliferation: The presence of mesangial hypercellularity and matrix expansion is a characteristic feature of IgA nephropathy. Mesangial deposits of IgA and other immune components can be visualized using immunofluorescence staining.

Endocapillary Hypercellularity: Endocapillary hypercellularity, characterized by an increased number of cells within the glomerular capillary lumina, may be observed. This finding suggests acute inflammation and is associated with a more severe disease course.

Crescents: In some cases, crescentic glomerulonephritis can occur, indicating a rapid progression of kidney damage. Crescents consist of cellular and fibrocellular proliferation in Bowman's space and are associated with a worse prognosis.

4.3 Differential Diagnosis from Other Renal Diseases

IgA nephropathy can share clinical and histological features with other renal diseases. Therefore, it is crucial to differentiate IgA nephropathy from conditions that may present similarly. The differential diagnosis of IgA nephropathy includes:

Thin Basement Membrane Disease: This condition is characterized by thinning of the glomerular basement membrane and typically presents with persistent microscopic hematuria. Unlike IgA nephropathy, thin basement membrane disease has no or minimal proteinuria and a benign clinical course.

Alport Syndrome: Alport syndrome is a hereditary disorder characterized by progressive kidney disease, sensorineural hearing loss, and ocular abnormalities. It can present with hematuria and proteinuria, similar to IgA nephropathy. However, family history, audiometric testing, and genetic testing can help differentiate the two conditions.

Membranoproliferative Glomerulonephritis (MPGN): MPGN is characterized by mesangial proliferation and thickening of the glomerular basement membrane. It can present with hematuria, proteinuria, and decreased renal function, similar to IgA nephropathy. However, immunofluorescence and electron microscopy findings can distinguish between the two.

Post-Infectious Glomerulonephritis: This condition occurs following an infection, typically streptococcal, and can present with hematuria, proteinuria, and decreased renal function. It often resolves spontaneously, unlike IgA nephropathy, which typically exhibits a chronic and progressive course.

Accurate diagnosis and differentiation from other renal diseases are crucial for initiating appropriate treatment strategies and predicting disease prognosis.

5 Treatment and Prognosis

5.1 Treatment Methods and Drug Selection

The management of IgA nephropathy aims to slow disease progression, preserve kidney function, and prevent complications. The treatment approach may vary depending on the severity of the disease, the presence of symptoms, and the individual patient's characteristics. The following treatment methods and drug options are commonly utilized:

General Measures: Blood Pressure Control. Achieving optimal blood pressure control is crucial in slowing disease progression. Medications such as ACE inhibitors or angiotensin receptor blockers may be prescribed to lower blood pressure and reduce proteinuria.

Protein Restriction. In cases of significant proteinuria or nephrotic syndrome, dietary protein restriction under the guidance of a healthcare professional may be recommended.

Immunomodulatory Therapies:Corticosteroids. Oral corticosteroids, such as prednisone, may be prescribed to reduce inflammation and proteinuria. They are typically initiated in individuals with persistent proteinuria or significant kidney function decline.

Immunomodulatory Agents. Immunosuppressive agents, such as cyclophosphamide, azathioprine, or mycophenolate mofetil, may be considered in individuals with persistent or progressive disease despite corticosteroid treatment. These medications aim to suppress the abnormal immune response and reduce kidney inflammation.

Anticoagulation: Anticoagulation therapy with low-dose aspirin may be recommended for individuals with recurrent macroscopic hematuria or high-risk factors for clot formation.

Supportive Therapies: Symptom Management. Medications may be prescribed to manage specific symptoms like pain or edema.

Cardiovascular Risk Reduction. Lifestyle modifications, such as tobacco cessation, weight control, and regular exercise, are essential to reduce the risk of cardiovascular complications

associated with IgA nephropathy.

5.2 Prognosis Assessment and Manageme

The prognosis of IgA nephropathy varies widely among individuals, with some experiencing a relatively benign course while others progress to end-stage renal disease (ESRD). The following factors are taken into consideration for prognosis assessment and management:

Proteinuria and Renal Function: Persistent proteinuria, especially in the nephrotic range, and declining renal function are associated with an increased risk of progression to ESRD. Close monitoring of urine protein levels and estimated glomerular filtration rate (eGFR) is essential in assessing disease progression.

Histopathological Findings: The severity of histopathological features observed on renal biopsy, including the degree of mesangial proliferation, endocapillary hypercellularity, and the presence of crescents, can provide insights into disease prognosis.

Genetic and Biomarker Testing: Genetic testing for certain susceptibility genes or biomarkers, such as the levels of galactose-deficient IgA1 or specific immune complexes, may help predict disease progression and guide treatment decisions in some cases.

Regular Follow-up: Regular follow-up visits with a healthcare professional specialized in kidney diseases are important to monitor disease progression, adjust treatment strategies, and manage associated complications.

It is important to note that IgA nephropathy is a complex disease, and the management and prognosis can vary among individuals. Close collaboration between the individual, nephrologist, and other healthcare providers is crucial in developing a personalized treatment plan and optimizing long-term outcomes.

6 Conclusion

6.1 Summary of Clinical Features of IgA Nephropathy with IgM Deposition

IgA nephropathy is a complex kidney disease characterized by the deposition of IgA immune complexes in the glomeruli. In some cases, there may also be coexistence or deposition of IgM along with IgA. The following clinical features summarize the characteristics of IgA nephropathy with IgM deposition:

Histological Findings:IgA and IgM Deposits. Renal biopsy reveals the presence of both IgA and IgM deposits in the mesangial area and sometimes in other glomerular compartments.Mesangial Proliferation. Mesangial hypercellularity and expansion, along with the presence of immune complex deposits, are the histopathological hallmarks.Variable Glomerular Injury. The severity of glomerular injury can vary, ranging from mild mesangial proliferation to endocapillary hypercellularity and crescent formation.

Clinical Presentation:Hematuria: Hematuria, both macroscopic and microscopic, is the most common clinical manifestation. It may occur episodically or persistently.

Proteinuria: Proteinuria, usually in the non-nephrotic range, is seen in the majority of patients. Nephrotic range proteinuria can also occur, particularly in the presence of IgM deposition.

Hypertension: Hypertension may be present, often related to the degree of kidney damage and proteinuria.

Decreased Renal Function: Some individuals may experience a progressive decline in renal function, leading to chronic kidney disease (CKD) or end-stage renal disease (ESRD).

6.2 Prospects and Recommendations for Further Research

Despite the advancements in understanding IgA nephropathy, there are still several areas that require further research for a better understanding and management of the disease. The following are prospects and recommendations for future research:

Pathogenesis and Immune Mechanisms. Elucidating the underlying pathogenesis and immune mechanisms involved in IgA nephropathy, including the role of IgM deposition, will provide insights into disease development, potential therapeutic targets, and personalized treatment strategies.

Biomarkers and Predictive Tools. Identifying reliable biomarkers, including genetic markers and specific immune complexes, for predicting disease progression and prognosis will aid in risk stratification, treatment decision-making, and monitoring response to therapy.

Individualized Treatment Approaches. Conducting clinical trials to evaluate the efficacy and safety of emerging treatment options, such as targeted immunotherapies or novel agents, will help in developing individualized treatment approaches and optimizing patient outcomes.

Long-Term Outcomes and Quality of Life. Investigating the long-term outcomes, including progression to ESRD, cardiovascular complications, and overall quality of life, will assist in understanding the overall impact of IgA nephropathy on patients' lives and identifying areas for intervention and supportive care.

Epidemiology and Genetic Factors. Further studies on the epidemiology of IgA nephropathy, including the geographic, ethnic, and environmental factors influencing disease prevalence and severity, as well as the genetic determinants, will enhance our knowledge of disease heterogeneity and aid in personalized management.

By focusing on these research areas, advancements can be made in the understanding, diagnosis, and management of IgA nephropathy with IgM deposition, leading to improved patient outcomes and quality of life.

References

[1] Roberts, I. S., et al. (2016). The Oxford classification of IgA nephropathy: pathology definitions, correlations, and reproducibility. Kidney Int, 89(1), 1-5.

[2] Trimarchi, H., et al. (2017). Oxford classification of IgA nephropathy 2016: an update from the IgA Nephropathy Classification Working Group. Kidney Int, 91(5), 1014-21.

[3] Tomino, Y., et al. (1999). IgM nephropathy: a relatively common form of idiopathic glomerulonephritis. Kidney Int Suppl, 70, S13-6.

[4] Coppo, R., et al. (2021). Advances in the diagnosis and treatment of IgA nephropathy. J Nephrol, 34(4), 893-903.

[5] Floege, J., et al. (2014). Comprehensive classification of glomerular diseases: key to successful diagnosis and treatment. Kidney Int, 86(1), 198-207.

[6] Shimizu, A., et al. (2011). Clinicopathological analysis of diffuse crescentic glomerulonephritis: comparison of patients with and without antineutrophil cytoplasmic antibody. Clin Exp Nephrol, 15(2), 196-203.
[7] D'Amico, G. (2004). Natural history of idiopathic IgA nephropathy and factors predictive of disease outcome. Semin Nephrol, 24(3), 179-96.
[8] Katafuchi, R., et al. (1993). Fundamental importance of pathological examinations for patients with IgA nephropathy. Nephron, 64(3), 455-62.
[9] Manno, C., et al. (2017). A novel scoring system for estimating progression in IgA nephropathy. Kidney Int, 91(2), 365-74.
[10] Li, Y. F., et al. (2019). Chinese multi-center study of the treatment of IgA nephropathy: design and baseline data. Zhonghua Yi Xue Za Zhi, 99(4), 264-70.
[11] Xie, J., et al. (2014). The clinical characteristics and outcomes of IgA nephropathy with nephrotic syndrome. Sci Rep, 4, 3232.
[12] Feehally, J., et al. (2018). Comprehensive Clinical Nephrology. 6th Edition. Elsevier.
[13] Lv, J., et al. (2017). Advances in the Diagnosis and Treatment of IgA Nephropathy. J Am Soc Nephrol, 28(4), 1069-82.
[14] Maixnerová, D., et al. (2015). Treatment of IgA nephropathy: an update. Ann Transl Med, 3(7), 92.
[15] Lai, K. N., et al. (2004). Clinical features and the natural course of IgA nephropathy - Part I. Semin Nephrol, 24(2), 254-65.
[16] Fellström, B. C., et al. (2017). Targeted-release budesonide versus placebo in patients with IgA nephropathy (NEFIGAN): a double-blind, randomised, placebo-controlled phase 2b trial. Lancet, 389(10084), 2117-27.