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IgA Nephropathy – selected problems including older patients

Nefropatia IgA – wybrane zagadnienia z uwzględnieniem chorych w wieku starszym

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S u m m a r y

IgA nephropathy (IgAN) is a proliferative form of glomerulonephirits with massive residues of IgA in mesangium. Presently it is the most frequently diagnosed form of glomerulonephritis in the world. It constitutes from 25% to 50% of all histopathological identifications of kidney biopsy specimens. This frequency varies according to the world region, which could depend on both real differences in its occurrence and on utilizing different indications in biopsy or diagnostic criteria. IgAN is above all a condition of the young people, and the peak of falling ill is during their twenties and thirties. It does occur in older patients as well. It is believed that the advanced age may be one of the factors causing quicker progression of the kidney disease. In literature not much information can be found concerning IgA nephropathy in older patients. It may result from the fact that the basis for diagnosing glomerulonephrititis is kidney biopsy. However, in older patients reluctance to having a kidney biopsy performed is quite common, mostly due to fear of complications. In this paper available data concerning IgAN epidemiology was summarized, including both general population and the population of seniors. Moreover, the level of knowledge in regard to prognosis and the strategy of therapeutic actions while taking into account older patients' population was discussed.

Key words: IgA nephropathy, epidemiology, prognosis, treatment, older patients

S t r e s z c z e n i e

Nefropatia IgA (IgAN) jest to rozplemowa postać kłębuszkowego zapalenia nerek (KZN) z masywnymi złogami IgA w mezangium. W chwili obecnej jest to najczęściej rozpoznawana postać kłębuszkowego zapalenia nerek na świecie. Stanowi od 25 do 50% wszystkich rozpoznań histopatologicznych bioptatów nerek. Ta częstość jest różna w poszczególnych regionach świata, co może zależeć zarówno od rzeczywistych różnic w występowaniu, jak i stosowaniu odmiennych wskazań do biopsji i kryteriów diagnostycznych. IgAN jest chorobą przede wszystkich ludzi młodych, szczyt zachorowań przypada na drugą i trzecią dekadę życia. Spotykana jest również u pacjentów starszych. Uważa się, że zaawansowany wiek może być jednym z czynników doprowadzających do szybszej progresji choroby nerek. W piśmiennictwie niewiele jest doniesień na temat nefropatii IgA u starszych pacjentów. Wynikać to może z faktu, że podstawą rozpoznania kłębuszkowych zapaleń nerki jest biopsja nerki. Natomiast u pacjentów starszych powszechna jest niechęć do wykonywania biopsji nerki, głównie w obawie przed jej powikłaniami. W niniejszej pracy podsumowano dostępne dane na temat epidemiologii IgAN w populacji ogólnej oraz w populacji ludzi starszych. Omówiono również stan wiedzy dotyczący rokowania i strategię postępowania terapeutycznego z uwzględnieniem populacji pacjentów starszych.

Słowa kluczowe: nefropatia IgA, epidemiologia, rokowanie, leczenie, pacjenci starsi

INTRODUCTION

IgA nephopathy (IgAN) is a proliferative form of glomerulonephritis with massive residues of IgA in mesangium, which are frequently accompanied by residues of IgG, IgM, complement component C3 and membrane attack complex (MAC) (1).

IgAN was first described by Berger and Hinglais in 1968. Presently, it is the most frequently diagnosed form of glomerulonephritis in the world. It constitutes from 25 to 50% of all hitopathological identifications of kidney biopsy specimens. This frequency varies with regard to the particular world region, which may depend on both real differences on occurrence and utilizing different biopsy indications or diagnostic criteria. In Asian countries (Japan) IgA nephorpathy constitutes 50% of all glomerulonephritis instances, while

in Europe it is from 10 to 25%. In the United States it is merely a few percent (2, 3). In Poland the frequency of IgAN occurrence is about 15-20% (4). Such variations in occurrence frequency could suggest genetic basis. In Japan, due to high frequency of the disease in children and young adults between the ages of 6 and 18, urine screening tests are performed, whose aim is to detect symptoms of the disease (5).

ETIOPATHOGENESIS

IgA nephropathy is the primary glomerulonephritis, but IgA residues may be confirmed by performing a kidney biopsy also during other diseases. Secondary deposits of IgA may occur in kidneys in i.a. coeliac disease, liver diseases, diabetes, chronic rheumatic arthritis, nonspecific inflammatory bowel disease, during progress of HIV, HBV, lymphomas and paraneoplastic syndromes in progress of lung and large intestine cancer (4).

IgAN is considered a disease of immunological complexes. In 50-70% of adult patients and in about 8-16% of children an elevated level of IgA is observed in blood serum (6). *In vitro* studies provided information that lymphocytes in peripheral blood circulation in patients with IgAN produce more IgA than the lymphocytes of healthy patients (7).

IgA occurs in two subtypes: IgA1 and IgA2. In blood serum 90% of total IgA is IgA1, while IgA2 is present in the tunica mucosa of digestive tract and respiratory system. IgA is secreted in digestive system and respiratory system in response to bacterial and viral antigens, moreover there is a potential correlation between infections in those systems and the development of IgA nephropathy. Identified specific antigens causing mesangial IgA deposits are a heterogenous group including: HSV, EBV, CMV and flu viruses, adenovirus, helicobacter pyroli, β-hemolyzing streptococci, Campylobacter, E. coli and food antigens (eg. gliadin/gluten). In response to those antigens, produced immunoglobulin A stimulates phagocytosis by means of Fc receptor localized on CD89 and it provokes the activation of the complement on the alternative or pectin pathway (8, 9).

IgA can occur as a monomer or a polymer (pIgA) connected with protein chain J. In healthy people most of their pIgA is produced by the immune system of tunica mucosa, however, iin patients with IgA nephropathy an elevated production of pIgA1 is observed in their bone marrow, while a decreased production is observed in tunica mucosa. Studies have shown that pIgA is the main component of the deposits in glomeruli. Such increased pIgA production is also noted in distant observation of patients with IgAN, in whom changes in urine remain, while it decreases during the period of clinical remission (ie. with demission of changes in urine: haematocyturia and/or albuminuria) (10, 11).

In patients with IgA nephropathy, IgA1 has an increased capability to join in larger conglomerates due to abnormal galactosylation in hinge region, so called O-glycosylation. This defect provides IgA1 with a more negative charge, which favors the deposition of IgA aggregates in mesangium and their bonding with fibronectin, laminin and collagen IV. In patients with IgA nephropathy beta 1,3-galactosyltransferase, responsible for attaching galactose to IgA, defect in B lymphocytes is observed. When healthy, IgA1 is catabolized in liver by merging with asialoglycoprotein receptor (ASGPR). In result of O-glycosylation, hepatic clearance of IgA1 is signifiantly lowered. The molecules of IgA1 with lower galactose content create immunological complexes which bond more easily with fibronectin, laminin and collagen IV in mesangium, and that provokes the origin of nonspecific inflammatory response, including the activation of complement C3, leading to the development of nephropathy (10-12).

Mesangial cells express increased activity of ASGPR and they are able to produce pIgA1 nad C3 in IgAN. Proliferation of mesangium cells in IgAN also occurs by means of stimulating transferrin receptor (TfR), which preferentially bonds pIgA1, IgA1 complexes and defectively glicosylated IgA1, it moreover causes secretion of interleukin 6 (Il6) and TGF-β (transforming growth factor-β) (13).

In the pathogenesis of IgAN, participation of immunological complexes IgA-IgG is observed. Their significantly higher level occurs in patients with IgAN when compared to the patients with other types of glomerulus.

Polymeric form of IgA1 induces the expression of genes in the renin-angiotensin system and TGF-β to a significantly greater extent than its monomeric form, which proves its participation in the progress of chronic inflammatory process and kidney fibrosis. TGF-β stimulates proliferations of mesangium cells, however impeding its secretion leads to decrease in accumulation of extracellular matrix proteins (10, 11).

In patients with IgA nephropathy mesangium cells produce platelet-derived growth factor (PDGF) and PDGF B chain, which stimulate mesangium proliferation. In the studies on experimental glomerulonephritis model it was shown that impeding secretion of these factors results in decrease in mesangium proliferation (10, 11).

In IgA nephropathy an elevated presence of macrophages CD68 in the inflammatory infiltration of the interstitium is observed together with an increase in local proliferation in animal experimental subjects, which plays a great role in immunological response, intensification of the inflammatory process in the kidneys and tubulointersitial lesion (10, 11).

In IgAN pathogenesis genetic predisposition is thought to have an important role. It was proven that there was a correlation between histocompatibility

antigens HLA Bw12, Bw35 and Bw37, as well as HLA DR1 and DR4, and the progress of IgA nephropathy. German studies have informed that about 10% of subjects with IgAN had one or more relatives with glomerulonephritis (14).

What is also described is the influence of polymorphism of angiotensin converting enzyme (ACE) gene and renin-angiotensin gene system on IgAN progress. The issue of most value for genetic studies of IgA nephropathy is so called ACE I/D polymorphism. "I" indicates insertion – the presence of intron 16, which in the final effect decreases ACE activity, while "D" stands for deletion, which is the lack of said intron leading to the increase in ACE activity. Genotype's property is that of forming ACE activity in tissues and plasma, and the highest activity was observed for homozygote DD. Angiotensin II, which originated due to ACE involvement, intensifies fibrosis and hypertrophy in target cells, including kidney. There, it stimulates collagen production, causes an increase in TGFβ and PDGF concentration in mesangium and epithelium of proximal convoluted tubules. It was proven that the frequency of genotype DD is significantly higher in patients whose clinical progress is characterized by quicker development of chronic kidney disease and can be a marker for unfavorable prognosis for the progress of IgA nephropathy. It was stated that patients with genotype DD and ID exhibit significantly higher albuminuria, sclerosis and adhesion with Bowman's capsule in the glomeruli, as well as tubulointersitial lesion when compared to patients with genotype II. It is thought that I/D polymorphism is related to the process of chronic kidney damage, however it does not influence the acute phase of this process (15).

DIAGNOSTICS

In light microscope a diffuse or segmented proliferation of mesangium is observed, and in more advanced stages – hardening of glomeruli and fibrosis of stroma. The condition of diagnosis is exhibiting mesangial residue of IgA.

Those residues may be accompanied by residues of IgM, IgG and C3. A third of studies under electron microscope state dense immunological residue and thinning of glomerular basement membrane (GBM). Histopathological changes are presented in table 1 (1).

CLINICAL IMAGE

IgA nephropathy is more frequent in men (3:1). Macroscopic haematuria is the most frequent manifestation of the disease, reported by 40-50% of patients. Haematuria may occur for the first timeduring or a few days after an infection of the upper respiratory tract, less frequently one of digestive tract, and it can recur during other infections. Urine usually is brown (not red) and it does not contain blood clots. First symptoms in adults occur in their twenties and thirties. Haematuria, on occasion together with pain in the loins area, can last from a few hours up to a few days. During an intense haematuria a decrease of glomeruli filtration is noted in about 40% of patients and usually it is irreversible.

In 30-40% of patients asymptomatic haematuria and albuminuria are sole symptoms of of IgA nephropathy and frequently isolated haematuria occurs without albuminaria. It extremely rare for albuminaria and nephrotic syndrome to express without haematuria. Nephrotic syndrome is observed in about 10% of patients. Arterial hypertension occurs in about 20-40% of patients. In clinical image an acute kidney failure can be observed. It is a result of great intensification of inflammatory changes, with extracapillary proliferation and crescents or a result of renal tubules obturation by erythrocytes during major haematuria. Both situations are relatively rare.

In previously undiagnosed cases first symptoms of the disease can be the symptoms of advanced chronic kidney failure, which is frequently accompanied by severe arterial hypertension (16).

EPIDEMIOLOGY

IgAN is first of all a disease of young people, peak of acquiring it is when they are in their twenties or thirties. It can also be observed in older patients. It is thought that advanced age can be one of the factors leading to fast progression of kidney disease.

There is not much information in literature concerning IgA nephropathy in older patients. It may result from the fact that the basis for diagnosing glomerulonephritis is kidney biopsy. However, in older patients reluctance towards kidney biopsy is quite common, mostly due to their fear of complications. It is contradicted by the results of analysis of

Table 1. Histopathological changes in IgA nephropathy according to Hass.

	Classification	Histopathological features	10-year life span of kidney function (%)
I.	Minimum changes	Minimum proliferation in mesangium.	90
II.	Focal segmental hardening	Resembles primary FSGS without the crescents.	90
III.	Focal profilerative glomerulonephritis	< 50% of glomeruli with proliferation, a possibility of crescents, majority of lesions is segmental.	55
IV.	Diffuse proliferative glomerulonephritis	> 50% of glomeruli with proliferation, a possibility of crescents.	20
V.	Advanced chronic glomerulonephritis	> 40% of fibrated glomeruli and > 40% of tubules atrophy.	20

complications which occurred after an Indian study (17). 210 patients underwent a biopsy, including 26 in advanced age (61 to 78). One of the most frequent complication in older patients was haematuria (4 in 26 patients when compared to 7 in 186 among younger patients). Three patients had haematuria for one – two days and one patient for a week. Among older patients haematuria of such intensification was not observed that it would require blood transfusion or cause hemodynamic disorders. This group did not exhibit such complications as haematoma or the need of surgical intevention. In literature it is emphasized that prior to kidney biopsy in older patients one cannot suddenly lower blood pressure with calcium blockers because it can cause bleeding as a result of vasodilation of the intrarenal vessels changed with age and inhibiting platelet functions (18).

An interestin epidemiological study analyzing the frequency of occurrence of glomerulonephritis in one region in France inhabited by nearly 400 thousand caucasian people is a study published by Simon et al. (19). During 14 years 942 kidney biopsies were performed there, and primary glomerulonephritis was diagnosed in 480 patients (51%). IgAN was the most frequently observed type of nephropathy (33,4%) in those patients. Diffusion of this glomerulonephritis was 1.9 in 1,000 citizens, 3.3 in 1,000 men and 1 in 1,000 women. The difference in the frequency of occurrence depending on sex was strongly marked in the population between the ages of 10 and 19, while the weakest differences were observed between the ages of 60 and 79. IgAN is the most frequent type of glomerulonephritis up to the age of 59, however, at the ages 60 to 79 the most frequent type of glomerulonephritis is membranous nephropathy, rapidly progressive glomerulonephritis and IgAN. In the mentioned study IgAN and rapidly progressive glomerulonephritis are the most frequent causes of irreversible chronic kidney failure.

Another epidemilogical study analyzing frequency of glomerulonephritis occurrence in one of the regions of China is a study published by Wu et al. (20). In the period of 5 years 1550 kidney biopsies were performed, based on which primary glomerulonephritis was diagnosed. IgAN was second most frequent type of nephropathy diagnosed (24.5%) in all biopsied patients. However in the group of senior patients older than 60 (N = 42 subjects) it was diagnosed in only 9.5%. Authors of this study do not provide the information concerning criteria for biopsy in older patients. However, in the whole biopsied group nephrotic syndrome occurred in 60% of patients.

Next epidemiological study analyzing frequency of glomerulonephritis in older patients in Irish population is a study published by Brown et al. (21). In the period of 5 years 1372 kidney biopsies were performed there, including 234 (17%) on patients older than 65. The oldest patient was 90 years old. The most frequent biopsy indications were: acute kidney failure (32%), nephrotic syndrome (25%), albuminuria (8%). Other, more rare causes were elevated creatinine concentration, exacerbation of chronic kidney failure, diabetes, arterial hypertension. In studied population of older patients IgA nephropathy was diagnosed in 7.6% of patients (as fourth most frequent) and was significantly more rare diagnosis than rapidly progressive glomerulonephritis (17.4%), tubulointerstitium diseases (11%), membranous glomerulonephritis (9%). Authors of this study do not analyze treatment in those patients. However, they summarize that a group of 102 patients who under observation having a biopsy had a creatinine concentration of 427 umol/L, and after three years a mean of 192 umol/L. Authors in their final conclusions emphasize a very crucial role of kidney biopsy also in the group of older patients, which according to them is important not only in diagnosis but it significantly influences prognosis and treatment.

Presently, we do not have such detailed study at our disposal concerning Polish population. Great hopes of obtaining epidemiological data are connected with efforts put into founding Polish Register of Nephropathy.

Observations concerning differences in clinical and pathomorphological image of younger and older patients with IgAN are published in literature.

One of such studies concerning Polish population analyzed a group of 64 patients with IgA nephropathy, where 14 patients was older than 45 (22%). In all patients haematuria and haematocyturia were observed. A detailed analysis revealed that in younger patients intense haematocyturia was more frequent. Albuminuria of various intensity occurred in almost every patient. However, proteinuria of medium and high level predominated in the group of older patients. Creatinine concentration above 1.5 mg/dl was comparable in both groups. Arterial hypertension occurred in statistically significant manner in the group of older patients. In microscopic study of renal biopsy specimens in all patients extensive, proliferative, mesangial glomerulonephritis of various degree of intensity of changes in glomeruli and interstitium was diagnosed. Intensification of mesangial proliferative changes in glomeruli was more frequent in younger patients, however, in older patients adhesion and agglutination in the glomeruli area was observed. Segmental or complete hardening of glomeruli was more frequent in the group of older patients. Similarly, in the group of older subjects a considerable atrophy of tubules and focal proliferation of connective tissue in intertisium as well as features of arterioles hardening were observed statistically significantly more frequently. Authors of this study in their summary state conclusions consilient with data available in literature, that

differences shown in both groups of subjects concerning intensification of clinical changes (higher albuminuria and higher proportion of hypertension in the group of older patients) and differences in the degree of kidney lesions (particularly greater intensification of interstitium changes in the group of older patients) support a worse prognosis in this group of patients.

In prospective study of Frimat et al. (23) concerning French population in the vicinity of Nancy, clinical image and disease progress of patients with IgA nephropathy over 50 (mean age about 62) – a group of 96 patients, and under 50 (mean age about 30) – a group of 33 patients – were compared. Older patients originally (at the time of the kidney biopsy) had higher contractile arterial pressure readings, higher albuminuria and lower creatinine clearance than younger patients. In this study no significant, statistically important differences were stated in kidney biopsy specimens between both groups, older patients had more intense changes in arteries. During a 40 month observation there were significantly more deaths in the group of older patients than younger ones (respectively 5 vs. 1 death) for reasons other than nephrological. There were no differences in the progress of chronic kidney disease in both groups, and the final point ie. the necessity of renal replacement therapy (dialysis or kidney transplant) reached a comparably identical proportion of subjects in the group of younger and older patients (15% vs 18% – differences not statistically significant).

Another study concerning Thai population (24) analyzed a group of 99 patients with IgA nephropathy, within which 82 subjects were classified as younger (mean age about 30), and 17 as older (mean age about 72). In the group of older patients arterial hypertension was more frequent than in younger ones (88% vs 30% of younger ones), nephrotic albuminuria (70% vs 27% in younger ones) and acute renal failure (53% vs 12% in younger ones). However, in the group of younger patients the most frequent manifestation of the disease was isolated haematuria or haematocyturia with non-nephrotic albuminuria. In biopsy specimens study older patients had a greater percentage of glomeruli sclerosis than the younger ones. In the group of patients with acute renal failure there were no differences between the two age groups concerning the instances of haematuria, intensification of albuminuria and the degree of advancement of chronic kidney disease at the moment of having the biopsy. However, older patients had a greater proportion of diseases coexisting with renal failure, in majority, bacterial infections. Four out of nine patients (4/9) in the older group died in the course of the disease, but there were no deaths in the younger group. In their summary the authors point that older patients with IgAN are characterized by significantly more serious and escalated clinical progress of this disease, particularly if acute renal failure occurs, and due to this fact their prognosis is worse.

In literature, there are also single reports of IgA nephropathy in older patients, whose clinical course was characterized by rapidly progressing glomerulonephritis (RPG). Mateu et al. (25) described a case of 78-year-old patient with RPG, who required renal replacement therapy of hemodilysis, and whose clinical improvement was obtained by administering pulses of glucocorticosteroids.

To summarize hitherto published studies concerning IgAN epidemiology in the population of older patients it needs to be stated that it occurs significantly less frequently in older than in younger patients. Perhaps the reason for it are significantly smaller groups of patients who had a kidney biopsy performed at an older age. Most frequent recommendations for kidney biopsy in older patients were acute renal failure and nephrotic syndrome, which are not the symptoms characteristic for IgA nephropathy.

PROGNOSTIC FACTORS

Nephropathy progress is generally either benign or very fast. After 20 years this disease leads to renal failure (5^{th} stage of chronic kidney disease) in 20-25% of patients, another 20% of patients is characterized by constant, progressive decrease of glomerulus filtration. There are also instances of fast deterioration of kidney function, with extracapillary proliferation dominating the microscopic image. In 60% of patients with nephrotic syndrome, after 10 years chronic renal failure develops (16).

Due to varied clinical symptoms it is not easy to predict the risk of nephropathy progression in particular patients. Based on numerous studies and observations factors of bad prognosis were selected. One of them is persistent albuminuria > 1.0 g/24 h. Moreover, elevated concentration of creatinin at the diagnosis is an independent factor for developing chronic renal failure. Only in about 10-20% of patients with creatinin concentration < 1.3 mg/dl at the diagnosis progression of chronic kidney disease occurs after 10 years. However, if patients have impaired glomerulus filtration at the diagnosis (ie. creatinin concentration above 1.3 mg/dl), 70-80% of them will develop chronic kidney disease after 10 years. It is believed that critical concentration causing irreversibility of the process is creatinin concentration above 3 mg/dl (16).

Other factors of bad prognosis for disease progress are older age at the diagnosis, lack of macroscopic haematuria (which may delay diagnosis), arterial hypertension, sex – male, overweight and smoking.

Histological exponents of bad prognosis are: a large percentage of glomeruli with crescents, glomeruli sclerosis and interstitium fibrosis, atrophy of renal tubules, deposits of IgA in capillary loops, as well as intramembranous deposits.

Among deviations in laboratory studies those of cancerous significance are: hyperlipidemia, hyperuricemia, insulin resistance exponents, as well as increased excretion with urine of Il-6 and tubulointerstitial lesion markers (α1-microglobulin) (16).

TREATMENT

Treatment depends on the size of albuminuria and GFR value at the beginning of treatment.

First step in treatment is lowering albuminuria by administering medication inhibiting renin-angiotensin, ie convertaze inhibitors (ACEI) or type 1 receptor antagonists for angiotensin II (sartans) (26). Presently, according to the newest guidelines of Polish Hypertension Society, target blood pressure should be about 130/80 mmHg and there is no proof supporting the idea of aiming at lower pressure readings in patients with nephropathy, even with significant albuminuria. However, results of studies such as MDRD or INVEST suggest that obtaining lower readings of arterial blood pressure may be in perspective favorable in the progress of nephropathy.

A positive influence of using ACEI in IgA nephropathy therapy was consilidated by results of a study with randomization published by Praga et al. (27). There, it was proven that administering enalapril in doses from 5 mg to 40 mg per 24 h was advantageous when compared with other antihypertensive medication while providing similar readings in blood pressure. In the group that was administered enalapril a decrease in albuminuriafrom 2.0 ± 1.3 to 1.2 ± 1.1 g/24 h was observed in the mean period of 7.5 years, while in the group that was administered placebo such effect was not observed. The probability of avoiding a significant loss of GFR in 7 years (increase in creatinin concentration above 50% in relation to the original reading) was 92% in the treated group and 55% in the placebo goup. Such results were thought to be connected with additional nephroprotective actions of ACEI blocking renin-angiotensin system, mainly through decreasing albuminuria.

After refuting COOPERATE study results, which evaluated joint therapy with ACEI (trandolapril) and sartan (losartan), there are no available studies confirming therapeutic efficiency of joining those two medication groups in therapy of not only IgA naphropathy but also other types of glomerulonephritis.

It is postulated that all patients of medium and high progression risk (ie. with albuminuria > 0.5-1.0 g/24 h and/or impaired glomerular filtration and/or arterial hypertension) should undergo so called optimal sustaining therapy, according to treatment chart presented below (28).

Algorithm for sustaining treatment in IgA nephropathy.

Level 1 of recommendations:

- Arterial blood pressure control;
- Administering ACEI or ARB;
- Adding dihydropyridine calcium channel blockers (in case of not obtaining target blood pressure readings), the aim of this therapy is efficient lowering of blood pressure as a means of decreasing albuminuria;
- Control of protein ingesting in the diet.

Level 2 of recommendations:

- Restricting sodium in the diet;
- Introducing diuretic treatment;
- Non- dihydropyridine calcium channel blockers;
- Controlling all components of metabolic system;
- Treatment with aldosterone antagonists;
- Treatment with beta-blockers;
- Ban of smoking;
- Allopurinol treatment;
- Empiric employment of $NaHCO_3$, regardless of whether metabolic acidosis occurs or not.

If, despite a few months treatment with ACEI or ARB, albuminuria is above 1 g/24 h or if there is a glomerular filtration loss of 5-10% a year, the next recommended step in pharmacological proceedings is a 6-month prednisolone therapy. Such action was proven in randomized study by Pozzi et al. (29). It bases on administering intravenous doses of methylprednisolone 1.0 g everyday for three days in 1st, 3rd and 5th month of therapy, as well as orally of prednisone in 0.5 mg/kg dose for six months. It needs to be particularly emphasized that this treatment chart and its effectiveness provided long lasting results. Decrease in albuminuria to below 1 g/24 h was observed after one year, which was six months after completing therapy, in 72% of subjects treated with prednisone and only in 30% of control subjects. During a ten-year observation in 97% of treated patients doubling of creatinine concentration did not occur, while this effect was observed in only 53% of control subjects.

In two studies by Manno et al. (30) and Lv et al. (31) charts with administering of oral prednisone were used. In the first study prednisone was administered for six months, in 1 mg/kg/d dose for two moths, when the dose was reduced by 0.2 mg/kg/d for a month. All patients were administered ramipril as well. It resulted in decreased reduction of GFR: 0.6 ml/min in the treated group when compared to 6.2 ml/min in control group. In the study of Lv et al. prednisone was administered for 6-8 months, in 0.8-1 mg/kg/min dose for 2 months, then the dose was reduced by 5-10 mg every two weeks. This chart also resulted in decreased GFR loss in the group treated with prednisone.

In two studies of Katafuchi et al. (32) and Hogg et al. (33) a favourable effect of prednisone on kidney function was not proven. In the first study small prednisone doses of 20 mg/24 h were administered and they were being reduced until 5 mg/24 h for 18 months. In the latter study prednisone was administered in the starting dose of 60 mg/m^2 for three months, then 40 mg/m^2 for nine months and finally 30 mg/m^2

for 12 months. Taking into account aforementioned reports it seems that the chart of Pozzi et al. with administering pulses of methylprednisolone is the most effective.

In the clinical situation in which albuminuria above 1 g/d is accompanied by progressing glomerular filtration defect > 10% a year it is recommended to introduce complex programs of immunosuppressive treatment. Data concerning effectiveness of such actions derive from randomized study by Ballerdie and Roberts (34) in a group of 38 patients with IgA nephropathy and with progressing glomerular filtration loss, expressed in the increase in creatinine concentration in serum in the period of 12 months prior to the study by at least 15%. Immunosuppressive treatment program included prednisone in the starting dose of 40 mg and gradually reducing it to 10 mg in the period of two years, oral cyclophosphamide in the dose of 1.5 mg/kg and replaced after three months with azathioprine 1.5 mg/kg/24 h administered for at least two years. In the treated group a significant decrease in albuminuria (from starting values of 3.9 ± 0.8 to 0.7 ± 0.27 g/24 h after 24 months) and haematocyturia was observed in the treated group. At the same time in the treated group a significant deceleration of glomerular filtration loss from 5 ml/min to 1 ml/min, however, in the placebo group no improvement was observed. In the final effect more than 70% patients who underwent treatment live through five years without progression of chronic renal failure, while such progression did appear in all patients from the control group. Due to the fact the group was small effectiveness of this chart has been recently discussed by eg. Floege and Eitner.

In 2010 Pozzi et al. (35) published results of randomized study conducted on a group of 207 patients with IgAN, who in addition to previously applied chart with pulses of methylprednisolone were also administered azathioprine in the dose of 1.5 mg/kg/24 h for six months. In a five-year observation benefits of applying broadened immunisuppressive chart were not reported.

In two Japanese studies, deriving from the same centre of pediatric population, the first applied glucocorticosteroid treatment in correlation with azathioprine and anticoagulant, while in the control group only anticoagulant was administered (36); in the latter study control group was administered prednisone, while treated group was administered prednisone, azathioprine and anticoagulant treatment (37). In both studies joint therapy influenced albuminuria reduction, without any influence on kidney funcition.

In several clinical studies of IgAN treatment, mycophenolate mofetil (MMF) was used in treatment. Only in a Hong Kong clinical trial conducted on Asian race its positive therapeutic effect was reported (38, 37). Patients with albuminuria above 1 g/24 h, who did not respond to conventional ACEI or sartan therapy, qualified for this study. Patients were randomized into two groups of 20 patients each: 20 patients administered wit MMF for 24 weeks (without gucocorticosteroids) and 20 patients administered with conventional treatment. In the group of patients administered with MMF in the dose of 1.5-2.0 g/24 h decrease in albuminuria by at least 50% was observed when compared to the control group. This effect lasted for the next 72 weeks. Differences in kidney function were not observed in neither group – the one treated with MMF or with conventional treatment.

Contrary results with applying MMF were reported in a study conducted in Belgium and the United States on Caucasian patients. In the Belgian study (40) MMF was being administered for three years in studied group in the dose of 2 g/24 h (21 subjects), and the control group consisted of 13 patients, however, all patients underwent ACEI treatment. During three-year observation no positive effect of decreased albuminuria or improving GFR was reported. American study (41) included 32 patients with albuminuria above 1 g/24 h and mean creatinine concentration of 2.4 mg/dl. Patients were randomized into the group administered with MMF in the dose of 2.0 g/24 h for 12 months (17 patients) and in to the control group (15 patients). All patients were administered ACEI. During a 24-month observation clinical progression in both groups was comparable, no positive effect on albuminuria decrease or improving GFR was reported. The authors concluded that perhaps MMF is not effective in patients with moderate kidney function disability.

In relation to presented study results it can be concluded that do not entitle to routine administering MMF in IgAN therapy, moreover, in order to determine MMF role in therapy, conducting a large scale randomized study is crucial.

There is no undoubtedly proven positive effect of other immunosuppressive medication in IgA nephropathy treatment. Beneficial effect of cyclosporine use was not reported.

There is no definite proof of positive influence of fish oil in IgAN patients treatment. However, published study results by Donadio et al (42), which showed positive influence of administering fish oil on kidney function. Moreover, in a small Italian study (43) a positive influence of administering fish oil on albuminuria reduction was proven, however, the fact that control group patients (not treated with fish oil) had originally worse prognostic factors (lower GFR, higher albuminuria, majority of men), may cause a constriction in the interpretation of the results of this study.

Antiplatelet therapy and anticoagulant treatment is frequently used in Asia. Small randomized study, in which dipridamole (75 mg three times a day) and warfarin (INR 1.3-1.5) were administered, proved a positive effect in the treated group when compared with the control group (44). Other stud-

ies utilizing antiplatelet treatment were retrospective and nonstandarized, while treatment was correlated with glucocorticoids. Hence, presently there are no recommendations for routine antiplatelet treatment or anticoagulant treatment.

Tonsillectomy, joint with immunosuppressive treatment is frequently recommended in Japan in patients with the risk of IgAN progression, however it is based on restrospective studies (45, 46). In one of the studies published by Komatsu et al. (47) it was proven that tonsillectomy correlated with glucocorticosteroid treatment is more efficient in achieving albuminuria and/or haematorcyturia remission than solely glucocorticosteroid treatment. However, there are no documented positive influences of tonsillectomy in Caucasian subjects (48, 49). That is why tonsillectomy is not generally prescribed in IgAN treatment. Recommendation for removing palatal tonsils appear when haematuria recurrence are visibly correlated with tonsil inflammation, while kidney function is preserved and advancement of histological changes is moderate (sclerosis includes < 25% of glomeruli).

An interesting remark from a Finnish study (50) is pointing to the relation between alcohol consumption and IgAN progression. A better kindey function was connected with restricting alcohol consumption in women (one cocktail/24 h) and in men (1-3 cocktails/24 h).

To summarize results of the aforementioned studies, the following chart for therapeutic conduct in patients with IgA nephropathy, depending on the risk of chronic kidney disease progression determined by the amount of albuminuria and glomerular filtration, could be accepted.

In case of low risk (ie albuminuria is lower than 0.5 g/24 h and GFR is higher than 60 ml/min/1,73 m^2) observation is recommended.

In case of moderate risk (albuminuria is 0.5-1.0 g/24 h and GFR is higher than 60 ml/min/1.73 m^2) administering medication from converatase inhibitors group or sartans, as well as restrictin salt consumption and reaching correct body mass is recommended.

However, if albuminuria is 1.0-3.0 g/24 h and GFR is higher than 60 ml/min/1.73 m^2 methylprednisolone i.v. is recommended in the dose of 1.0 g for three days, followed by prednisone in the dose of 0.5 mg/kg for six months.

In the case of highr risk of chronic kidney disease progression (ie if albuminuria is above 3.0 g/d and/or GFR is higher than 60 ml/min/1.73 m^2) in treatment cyclophosphamide and azathioprine are administered.

Based on available literature there are no detailed instructions concerning therapeutic conduct in older patients with IgA nephropathy. For this group one should apply therapeutic recommendations as for all patients with IgA nephropathy as described above.

Applying immunosuppressive treatment may raise doubts. One needs to remember that older patients are more prone to complications from glucocorticosteroids. Particularly in this group of patients quite common are such complications as: retaining sodium, swelling, arterial hypertension, the risk of post steroid diabetes , infectious complications. In older patients an increase in cortisol concentration and weaker reaction to adrenocorticotropic hormone occur. Hence, they exhibit an abnormal reaction to stress both during their ilness and after steroid treatment (52, 53).

That is why in older patients higher doses of steroids should be avoided, and doses of cytostatics should be adjusted to the patient's age, because the risk of complications is significantly higher. Due to this fact it is necessary to monitor morphological blood picture, liver function and the risk of acquiring osteoporosis (53).

When administering immunosuppressive treatment in older patients one needs to remember that actual age is not the main criterion for qualifying to therapy. It seems that biological age is more important together with patient's coexisting risk factors and other chronic diseases (54).

However, there are reports of positive results of administering cyclophosphamide in 30 older patients with glomerulonephritis progressing with nephrotic syndrome (55). In the studied group there were only three patients with IgA nephropathy. In most patients complete or partial remission was achieved. No infectious or thrombotic complications were observed. In one patient leukopenia was diagnosed and in two patients – cancers (liver and pleura, so the types of cancer not listed among those connected with administering cyclophosphamide).

There is no data concerning efficiency of using azathioprine in older patients with IgA nephropathy. There are only reports of using azathioprine when treating patients with membranous nephropathy, however, remarks are posed about its low efficiency and high risk of complications (56).

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