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Membranous glomerulonephritis – gender-related differences of disease course and evaluation of therapy efficiency

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Мембранозный гломерулонефрит – половые различия течения болезни и оценка эффективности терапии

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Abstract

Membranous glomerulonephritis (MGN) is the most common glomerular disease leading to nephrotic syndrome in adults. MGN can be primary (idiopathic) or secondary to other diseases. The treatment of MGN can be pathogenic or symptomatic. Pathogenetic treatment is indicated to patients with iMGN or class 5 lupus nephritis and includes a wide range of drugs: corticosteroids, alkylating agents, cyclosporine, tacrolimus, mycophenolate mofetil, ACTH and newer substances, products of gene engineering, such as rituximab and eculizumab.

The aim of this study was to evaluate the gender-specific differences in the disease course and to evaluate the effect of the therapeutic schemes in patients with biopsy-proven MGN.

We studied 72 subjects with biopsy-proven MGN. The levels of proteinuria, total plasma protein, albumin and renal function were examined at the time of the diagnosis, in its course and at the end of the follow-up. These markers were compared to gender, age, comorbidities and different treatment regimens.

We found statistically significant gender-related differences in the levels of proteinuria, total plasma protein and albumin. There was a difference in the full remission rates between genders, but no significant gender difference in the patients that reaching any remission and in the relapse rates. No difference was observed between patients receiving lower doses and high doses of Cyclophosphamide.

The results of our study reveal that females have a more favorable disease course with lower proteinuria and a higher chance of reaching complete remission than males. Our data show that treatment with lower doses of Cyclophosphamide leads to equally good results in reducing proteinuria and achieving remission compared to high doses and pulse treatment is a valid option in the treatment algorithm of iMGN.

Резюме

Мембранозный гломерулонефрит (МГН) является наиболее распространенным громерулярным заболеванием, приводящим к нефротическому синдрому у взрослых. МГН может быть первичным (идиопатическим) или вторичным – ассоциированным с другими заболеваниями. Лечение МГН является патогенетическим или симптоматическим. Патогенетическое лечение включает в себя

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использование широкого спектра лекарственных препаратов: кортикостероиды, алкилирующие агенты, циклоспорин, такролимус, микофенолат мофетил, АКТГ и более новые препараты – продукты генной инженерии, такие как ритуксимаб и экулизумаб.

Целью этого исследования была оценка особенностей течения заболевания у пациентов мужского и женского пола, а также оценка эффективности использования терапевтических схем у пациентов с МГН, подтвержденных биопсией.

Мы изучили 72 пациента с подтвержденным биопсией МГН. Показатели протеинурии, общего белка, альбумина и функции почек были исследованы во время постановки диагноза, во время течения болезни и в конце наблюдения. Полученные данные по этим показателям использовались для последующего сравнительного анализа с учетом пола и возраста пациентов, наличия сопутствующих заболеваний и различных режимов лечения.

Мы обнаружили статистически значимые гендерные различия в уровнях протеинурии, в концентрациях общего белка и альбумина. Наблюдалось различие в показателях полной ремиссии между полами, но не было существенной гендерной разницы у пациентов, которые достигли какой-либо ремиссии и в частоте рецидивов. Не наблюдалось различий между пациентами, получавшими низкие дозы и высокие дозы циклофосфамида.

Результаты нашего исследования показывают, что женщины имеют более благоприятное течение заболевания с более низкой протеинурией и у них более высокий шанс достичь полной ремиссии. Наши данные показывают, что лечение низкими дозами циклофосфамида приводит к одинаково хорошим результатам по снижению протеинурии и достижении ремиссии по сравнению с высокими дозами, а "пульс-терапия" сверхвысокими дозами является допустимым вариантом в алгоритме лечения иМГН.

Ключевые слова: *мембранозный гломерулонефрит; протеинурия; лечение*

Introduction

Membranous glomerulonephritis (MGN) is the most common glomerular disease leading to nephrotic syndrome in adults [1]. MGN can be primary (idiopathic) or secondary. Idiopathic MGN (iMGN) is an antibody-mediated disease, characterized by an uniform thickening of glomerular basal membrane (GBM), caused by sub-epithelial deposits of immune complexes [2, 3]. Treatment of MGN can be conservative (symptomatic) or pathogenic, depending on proteinuria, renal function and the risk of progression. Symptomatic therapy includes a dietary regimen with restriction of protein intake (0.8 gr/kg ideal body weight/daily of high-quality protein) and control of blood pressure (target BP<125/75 mmHg), hyperlipidemia and edemas [4, 5].

When conservative treatment is considered inadequate, in patients with iMGN or class 5 lupus nephritis pathogenic treatment with immunosuppressive drugs should be initiated, and the assessment is based on proteinuria and renal function. As monotherapy is rarely effective in MGN, a treatment regimen involving more than one drug is usually initiated [6]. There are various schemes involving different groups of immunomodulatory agents. An approximate algorithm for the treatment of iMGN was published in Cattran D. Management of membranous nephropathy: when and what for treatment. J Am Soc Nephrol 2005; 16: 1188-1194 [7].

In patients with mild proteinuria (below 4 g/day) and normal renal function the initial treatment is conservative (ACEI±ARB, dietary protein restriction, maintaining BP≤125/75 mmHg) and proteinuria and renal function continue to be monitored. In patients with moderate proteinuria (≥4 to <8 g/day) and normal renal function the initial treatment is conservative, and patients are monitored for 6 months. If nephrotic range proteinuria persists or the renal function decreases, or complications occur pathogenic treatment with corticosteroids and cytotoxic agents is initiated. If that treatment is not effective, cytotoxic agents are replaced with Cyclosporine. Patients with heavy proteinuria (≥8 g/day) and/or decreased renal function can start with conservative treatment and be monitored for a shorter period of time. If there is no effect on proteinuria and/or renal function the first drug of choice is Cyclosporine and if it is not effective it can be replaced by corticosteroids/cytotoxic combination. Similar are the guidelines of KDIGO from 2012 [8]. Despite the multiple agents and treatment regimens, around 30% of patients with iMGN progress to end stage renal disease [9]. Moreover, the medications used in iMGN treatment, are often associated with numerous side effects, including diabetes mellitus, infertility, neoplasms etc. Newer alternative agents with fewer side effects are urgently needed, but there are still no such with proven efficacy in achieving lasting remissions and renal survival. Therefore, it is important to apply an individualized approach to treatment aimed at achieving remission while minimizing the side effects and complications.

Materials and methods

Study design and subject selection

For the period 01.2009-01.2017 we studied 92 patients with biopsy-proven MGN, mean age

54.37±15.37 years (18-77), 56 males and 36 females. Twenty patients (11 males and 9 females) were lost during follow-up period and were excluded from the statistical analysis. Overall 72 patients were included (mean age 52.56±13.99 years, 18 to 77 years, 45 males and 27 females). In all patients MGN was verified with histological examination of percutaneous renal biopsy material. MGN was classified as primary or secondary after pro-active investigations due to the presence of neoplasms, systemic connective tissue diseases and viral hepatitis (HBs-antigen, anti-HCV). The following *inclusion criteria* were used: Age ≥18 years; histologically proven MGN; proteinuria over 4 g/day at the beginning of treatment; Follow-up for at least 12 months.

During the follow-up period and for the purposes of this study, the terms "remission" and "relapse" are defined as follows: incomplete remission: normal total protein and albumin values, proteinuria 2.0-0.2 g/day and proteinuria reduction no less than 50% of its peak value; complete remission: normal values of total protein and albumin, proteinuria below 0.2 g/day; relapse: increase of proteinuria over 2.0 g/day after reaching any remission.

Clinical data collection

Detailed medical history and complete physical examination were performed in all patients. Creatinine clearance was calculated according to the CKD-EPI formula (mL/min/1.73 m^2). All individuals underwent detailed standard abdominal ultrasound evaluation (ESAOTE-MYLAB-60).

Table 1

Frequency of primary and secondary MGN in males and females

Gender	Statistics	Primary	Secondary	Total	p
Males	N	42	3	45	0,034
	%	67.7%	30.0%	62.5%	
Females	N	20	7	27	
	%	32.3%	70.0%	37.5%	
Total	N	62	10	72	
	%	100.0%	100.0%	100.0%	

Laboratory data collection

Venous blood and urine were taken at standard conditions with standard methods. Creatinine, total protein and albumin were investigated in serum and proteinuria was investigated in 24 hour urine samples; the values expressed in grams/24 hours.

Histological data

After signing informed consent, all patients underwent percutaneous puncture renal biopsy (PRB) (automated Gun system, 16/20 G biopsy needle, blind, with preceding ultrasound location of the left kidney) with subsequent standard histological and immunohistochemical evaluation plus Congo-red staining, if needed (to exclude amyloidosis), and electron microscopy, if indicated.

Statistical analysis

All data were analyzed using standard statistical package SPSS 16.0 and EXCEL for Windows, using: 1) Fisher`s exact test; 2) Mann-Whitney U-test; 3) Kruskal Wallis Test for; 4) ANOVA Repeated measures; 5) Friedman test.

Results

Overall 45/72 patients (62.5%) were males and 27 (37.5%) were females. Eleven were under 35 years (15.3%), 36-65 years were 46 (63.9%), over 65 years were 15 patients (20.8%); 62 patients had primary MGN and 10 (13.9%) had secondary MGN. The studied patients had the following comorbidities: hypertension – 65 (90.35%), diabetes mellitus – 23 (32%) in 9 (12.5%) the diabetes preceded the diagnosis of MGN and 14 (19.5%) the diabetes occurred in the course of treatment, 7 (9.7%) had systemic lupus, 3 (4.2%) – viral hepatitis. Ten patients (13.9%) were with secondary MGN and 62 (86.1%) had iMGN (Table 1).

In females, proteinuria was significantly lower (both at the onset of MGN and on subsequent measurements, Table 2). Similar gender-related difference was found in total protein and albumin levels (Table 3 and 4). There

Table 2

Proteinuria levels in male and female patients

Marker	Gender	N	Mean	Median	SD	Min	Max	U	p
Proteinuria 1*	Male	45	9.82	8.00	5.91	1.00	26.00	412.0	0.022
	Female	27	7.04	6.00	5.47	1.00	27.00		
Proteinuria 2*	Male	45	5.84	5.00	4.01	0.00	15.00	301.0	<0.001
	Female	27	2.78	2.00	2.41	0.00	9.00		
Proteinuria 3*	Male	45	4.67	3.00	4.69	0.00	19.00	351.0	0.002
	Female	27	1.85	1.00	1.96	0.00	7.00		
Proteinuria 4*	Male	45	3.69	2.00	5.20	0.00	27.00	385.5	0.008
	Female	27	1.52	0.00	2.49	0.00	9.00		

* 1 – initial proteinuria, 2 – proteinuria after initial treatment, 3 – proteinuria 6 months after end of initial treatment, 4 – proteinuria at the end of follow-up period

Table 3

Albumin levels in male and female patients

Marker	Gender	N	Mean	Median	SD	Min	Max	U	p
albumin 1 *	Male	45	24.00	24.00	7.19	10.00	40.00	464.0	0.095
	Female	27	27.04	27.00	7.33	10.00	40.00		
albumin 2 *	Male	45	29.51	30.00	6.27	14.00	40.00	317.0	0.001
	Female	27	35.22	36.00	5.88	25.00	43.00		
albumin 3 *	Male	45	32.98	34.00	6.34	16.00	44.00	438.5	0.049
	Female	27	36.07	37.00	4.46	27.00	44.00		
albumin 4 *	Male	45	35.20	36.00	7.76	15.00	48.00	528.5	0.357
	Female	27	37.15	38.00	5.33	25.00	47.00		

* 1 – initial albumin values, 2 – albumin values after initial treatment, 3 – albumin values 6 months after end of initial treatment, 4 – albumin values at the end of follow-up period

Table 4

Total protein levels in male and female patients

Marker	Gender	N	Mean	Median	SD	Min	Max	U	p
Total protein 1 *	Male	45	49.36	49.00	7.80	37.00	74.00	477.0	0.128
	Female	27	52.52	52.00	8.16	38.00	69.00		
Total protein 2 *	Male	45	54.20	55.00	7.75	41.00	70.00	355.5	0.003
	Female	27	60.56	59.00	7.24	45.00	75.00		
Total protein 3 *	Male	45	57.47	58.00	8.83	38.00	72.00	413.5	0.024
	Female	27	62.22	64.00	7.23	44.00	73.00		
Total protein 4 *	Male	45	60.60	63.00	10.01	39.00	80.00	532.5	0.382
	Female	27	63.04	62.00	8.05	46.00	78.00		

* 1 – initial total protein values, 2 – total protein values after initial treatment, 3 – total protein values 6 months after end of initial treatment, 4 – total protein values at the end of follow-up period

Table 5

Renal function in male and female patients

Marker	Gender	N	Mean	Median	SD	Min	Max	U	p
eGFR 1 *	Male	45	70.64	65.00	31.60	6.00	132.00	581.0	0.758
	Female	27	67.37	73.00	33.76	4.00	134.00		
eGFR 2 *	Male	45	70.87	78.00	31.64	9.00	129.00	538.0	0.419
	Female	27	65.37	63.00	24.01	14.00	109.00		
eGFR 3 *	Male	45	73.62	76.00	32.26	13.00	153.00	514.5	0.279
	Female	27	66.37	68.00	27.47	13.00	127.00		
eGFR 4 *	Male	45	66.38	62.00	29.46	5.00	121.00	578.0	0.731
	Female	27	67.96	77.00	32.02	8.00	121.00		

* 1 – initial renal function, 2 – renal function after initial treatment, 3 – renal function 6 months after end of initial treatment, 4 – renal function at the end of follow-up period

Table 6

Frequency of achieved remission (complete and partial) and no achieved remission in women and men with MGN

Remission	Statistics	Males	Females	Total	p
None	N	8	3	11	0.030
	%	17.8%	11.1%	15.3%	
Partial	N	23	7	30	
	%	51.1%	25.9%	41.7%	
Complete	N	14	17	31	
	%	31.1%	63.0%	43.1%	
Total	N	45	27	72	
	%	100.0%	100.0%	100.0%	

was no significant difference in eGFR in males and females (Table 5). We observed no correlation between the histological stage of the disease and gender.

In terms of remission, we observed no significant gender difference in achieving any remission. Full remissions occurred more frequently in females, while males more often achieved partial remissions. There was also a slightly higher incidence of males in patients who never reached remission, 18%, compared to 11% in females (Table 6). In patients who reached any remission, the incidence of relapses did not show gender-related differences. There was a significantly higher prevalence of the secondary forms in females (Table 1).

In terms of treatment, all patients were treated with at least two immunosuppressive drugs. There was no

Table 7

Frequency of diabetes mellitus (pre-existing and developed in the treatment course) in males and females with MGN

Gender	Statistics	Diabetes mellitus			Total	p
		No	Pre-existing	Developed in the course of treatment		
Male	N	30	9	6	45	0.01
	%	61.2%	100.0%	42.9%	62.5%	
Female	N	19	0	8	27	
	%	38.8%	0.0%	57.1%	37.5%	
Total	N	49	9	14	72	
	%	100.0%	100.0%	100.0%	100.0%	

statistically significant difference in the agents used in the treatment of primary and secondary forms, with the exception of Imuran (Azathioprine, AZA), which was mainly used in the treatment of secondary membranous nephropathy cases associated with lupus. In patients treated with Cyclophosphamide (CYC), the administered cumulative doses did not differ in primary and in secondary MGN.

In the subgroup with diabetes mellitus, such pre-existing glomerular disease was observed only in males (Table 7). In patients with diabetes mellitus developed in the course of treatment there, no difference between males and females was found (Table 7). There was a statistically significant difference in proteinuria levels after the initial ones in patients with and without diabetes mellitus, proteinuria being higher in diabetic patients (in diabetic patients mean proteinuria after initial treatment was 9.56 g/day±5.14, in non-diabetic patients it was 3.98 g/day±3.16, p=0.009). Accordingly, there were differences in total protein and albumin levels. Although no pathological features of diabetic nephropathy were described in this group, some discreet changes cannot be excluded. There was no difference between the groups in serum creatinine and eGFR levels (in diabetic patients mean eGFR was 67.74 mL/min/1.73 m^2±26.42, in non-diabetic patients mean eGFR was 77.11 mL/min/1.73 m^2±29.86, p=0.796).

All patients were treated with at least two immunosuppressive drugs – 49 (65.8%) were treated with a combination of two immunosuppressants, 16 (21%) patients were treated with three drugs and 7 (8.4%) were treated with four immunosuppressive agents. The majority patients (46, 65%) were treated with a combination of corticosteroid (GCs) (administered as pulse and then orally – p.o. – or only orally) and CYC (pulse, oral or combined). In 13 of them, a third immunosuppressive drug (in 7 – AZA and in 5 – Cyclosporine A, CsA) was added after no response to the initial treatment. In the

Table 8

Proteinuria levels in patients treated with CsA after lack of effect of initial treatment with GCs+CYC

Marker	CsA	N	Mean	Median	SD	Min	Max	U	P**
Proteinuria 1*	+	62	8.39	7.00	5.60	1.00	27.00	241.0	0.260
	-	10	11.20	10.00	7.21	3.00	25.00		
Proteinuria 2*	+	62	4.21	4.00	3.37	0.00	15.00	174.5	0.026
	-	10	7.70	6.50	4.95	2.00	15.00		
Proteinuria 3*	+	62	3.00	2.00	3.57	0.00	19.00	113.0	0.001
	-	10	7.40	5.00	5.36	3.00	16.00		
Proteinuria 4*	+	62	2.00	1.00	2.63	0.00	10.00	114.0	0.001
	-	10	8.30	4.50	8.59	1.00	27.00		

* 1 – initial proteinuria, 2 – proteinuria after initial treatment, 3 – proteinuria 6 months after end of initial treatment, 4 – proteinuria at the end of follow-up period
** significance of difference between patients treated with CsA and patients not treated with CsA

Table 9

Albumin levels in patients treated with CsA after lack of effect of initial treatment with GCs+CYC

Marker	CsA	N	Mean	Median	SD	Min	Max	U	P**
albumin 1*	+	62	25.73	26.00	6.83	10.00	40.00	205.0	0.087
	-	10	21.50	19.50	9.57	10.00	38.00		
albumin 2*	+	62	32.15	32.00	6.69	14.00	43.00	220.5	0.145
	-	10	28.60	30.50	6.17	18.00	37.00		
albumin 3*	+	62	34.79	36.00	5.50	19.00	44.00	181.5	0.036
	-	10	30.10	30.00	6.76	16.00	39.00		
albumin 4*	+	62	36.60	38.00	6.51	17.00	48.00	201.5	0.077
	-	10	31.80	30.00	8.57	15.00	46.00		

* 1 – initial albumin values, 2 – albumin values after initial treatment, 3 – albumin values 6 months after end of initial treatment,
4 – albumin values at the end of follow-up period
** significance of difference between patients treated with CsA and patients not treated with CsA

Table 10

Renal function in patients treated with CsA after lack of effect of initial treatment with GCs+CYC

Marker	CsA	N	Mean	Median	SD	Min	Max	U	P**
eGFR 1*	+	62	73.00	75.00	33.26	4.00	136.00	284.0	0.672
	-	10	66.80	56.50	26.12	29.00	106.00		
eGFR 2*	+	62	69.81	72.50	28.50	9.00	131.00	302.5	0.903
	-	10	69.80	73.50	33.31	9.00	127.00		
eGFR 3*	+	62	71.15	71.00	30.20	13.00	132.00	302.0	0.896
	-	10	76.20	74.00	34.03	35.00	155.00		
eGFR 4*	+	62	69.42	72.50	31.40	5.00	123.00	233.5	0.213
	-	10	59.00	55.50	20.50	36.00	110.00		

* 1 – initial renal function, 2 – renal function after initial treatment, 3 – renal function 6 months after end of initial treatment, 4 – renal function at the end of follow-up period

** significance of difference between patients treated with CsA and patients not treated with CsA

Table 11

Frequency of achieved remission (complete and partial) and no achieved remission in patients treated with different cumulative doses of CYC

Doses	Statistics	Remission			Total	p
		None	Partial	Complete		
<3500	N	4	11	9	24	0.619
	%	40.0%	40.7%	30.0%	35.8%	
3550-7000	N	5	8	14	27	
	%	50.0%	29.6%	46.7%	40.3%	
7050-10000	N	0	2	4	6	
	%	0.0%	7.4%	13.3%	9.0%	
>10000	N	1	6	3	10	
	%	10.0%	22.2%	10.0%	14.9%	
Total	N	10	27	30	67	
	%	100.0%	100.0%	100.0%	100.0%	

Table 12

Proteinuria levels in patients treated with different cumulative doses of CYC

Marker	Doses	N	Mean	Median	SD	Min	Max	Chi-Square	P
Proteinuria 1*	<3500	29	6.90	6.00	4.62	1.00	21.00	7.9	0.047
	3550-7000	27	11.33	9.00	6.69	3.00	27.00		
	7050-10000	6	7.67	8.50	4.18	1.00	13.00		
	>10000	10	8.00	6.50	5.83	2.00	22.00		
Proteinuria 2*	<3500	29	4.69	4.00	3.58	0.00	14.00	4.5	0.210
	3550-7000	27	5.22	5.00	4.05	0.00	15.00		
	7050-10000	6	2.00	1.00	2.00	1.00	6.00		
	>10000	10	4.90	3.50	4.23	0.00	15.00		
Proteinuria 3*	<3500	29	4.10	3.00	4.28	0.00	19.00	4.2	0.242
	3550-7000	27	2.93	1.00	4.03	0.00	16.00		
	7050-10000	6	2.17	1.50	2.48	0.00	7.00		
	>10000	10	4.90	3.50	4.56	1.00	14.00		
Proteinuria 4*	<3500	29	2.83	2.00	3.15	0.00	10.00	2.2	0.531
	3550-7000	27	3.00	1.00	5.78	0.00	27.00		
	7050-10000	6	1.17	1.00	0.75	0.00	2.00		
	>10000	10	3.70	2.00	5.31	0.00	18.00		

* 1 – initial proteinuria, 2 – proteinuria after initial treatment, 3 – proteinuria 6 months after end of initial treatment, 4 – proteinuria at the end of follow-up period

Table 13

Albumin values in patients treated with different cumulative doses of CYC

Marker	Doses	N	Mean	Median	SD	Min	Max	Chi-Square	p
albumin 1 *	<3500	29	27.03	29.00	7.84	10.00	40.00	3.7	0.292
	3550-7000	27	23.78	24.00	7.10	10.00	40.00		
	7050-10000	6	24.17	23.50	6.49	16.00	33.00		
	>10000	10	23.90	24.00	6.72	16.00	38.00		
albumin 2 *	<3500	29	30.55	29.00	7.52	14.00	43.00	3.0	0.388
	3550-7000	27	31.85	32.00	6.21	18.00	43.00		
	7050-10000	6	35.67	37.50	7.39	22.00	43.00		
	>10000	10	31.90	32.50	4.53	21.00	37.00		
albumin 3 *	<3500	29	33.31	34.00	6.00	20.00	43.00	3.9	0.277
	3550-7000	27	35.07	36.00	5.80	16.00	44.00		
	7050-10000	6	37.00	37.50	2.37	33.00	40.00		
	>10000	10	32.30	31.50	6.73	19.00	42.00		
albumin 4 *	<3500	29	33.55	35.00	6.69	17.00	43.00	6.1	0.107
	3550-7000	27	37.52	38.00	6.96	15.00	48.00		
	7050-10000	6	37.17	38.00	5.34	29.00	43.00		
	>10000	10	37.80	39.00	7.57	27.00	48.00		

* 1 – initial albumin values, 2 – albumin values after initial treatment, 3 – albumin values 6 months after end of initial treatment, 4 – albumin values at the end of follow-up period

remaining patients various combinations of immunosuppressive medications were used, all of which included corticosteroids and CYC and one or more other drugs.

When CsA was added to therapy, we observed marked effect on proteinuria, especially in the late stages of follow-up, and a corresponding, albeit less pronounced, increase in the levels of total protein and albumin (Table 8 and 9). The more pronounced effect in later stages of follow-up can be explained by the fact that CsA was included later in therapy when there was no effect from the initial treatment. No significant difference in renal function was observed compared to CsA-free patients (Table 10).

Table 14

Dynamics of laboratory parameters in patients with MGN at different periods of treatment

Marker	1-2	1-3	1-4	2-3	2-4	3-4
	p	p	p	p	p	p
Proteinuria*	<0.001	<0.001	<0.001	<0.001	<0.001	0.001
Total protein**	<0.001	<0.001	<0.001	<0.001	<0.001	<0.001
Albumin**	<0.001	<0.001	<0.001	0.002	<0.001	0.002
Creatinine*	0.961	0.644	0.760	0.832	0.201	0.016
eGFR**	0.798	0.595	0.389	0.265	0.423	0.051

** U-test; ** Post Hoc test – (Sidak)*

1 – initial value, 2 – value after initial treatment, 3 – value 6 months after end of initial treatment, 4 – value at the end of follow-up period

In patients on CYC we found no significant difference in remission rates at the different cumulative doses and the route of administration (i.v. and p.o.) (Table 11). No dose-related differences in proteinuria levels, total protein, serum albumin, and renal function were observed (Table 12 and 13). During the follow-up after initial treatment, we observed significant reduction of proteinuria and increase of total protein and albumin levels without statistically significant effect on renal function (Table 14).

Discussion

MGN is one of the most common glomerulopathies in adults. In approximately 30% of the patients the disease progresses and leads to terminal renal failure despite the treatment. One of the risk factors for progression is male gender. Our study confirms that MGN in women occurs with significantly lower levels of proteinuria, both at baseline and subsequent measurements [10]. In the studied patients, statistically significant differences between the two genders were reported at all proteinuria values, but in terms of total protein and albumin, such differences were observed in the interim measurements, but not at the beginning and end of the follow-up period. In our study there was a statistically significant difference in creatinine levels between males and females in all measurements but no difference in eGFR levels. This can be explained by the formula used for calculating eGFR (CKD-EPI), which does not take into account body weight and higher muscle mass in men.

Female gender is well-known factor favoring remission. In our study there was no difference in the total number of remissions, but reaching a full remission was significantly higher in female sex. Significant differences in the incidence of relapses in men and women were not found.

Our data showed a statistically significant prevalence of secondary forms of MGN in women. In interpreting these results, it should be borne in mind that the secondary MGNs in our study were based mainly on systemic lupus erythematosus (prevalent in women) and a few were associated with viral hepatitis, but not on neoplasms – patients with proven neoplastic diseases were directed for treatment of the underlying disease, and were lost from follow-up and therefore were not included in the statistical analysis.

The significant differences in the treatment of primary and secondary forms with AZA should be interpreted according to the data presented above. AZA is a purine antimetabolite and its effect in iMGN is controversial and it is not included in the commonly used treatment algorhythms. More commonly used in the treatment of MGN is mycophenolate mofetil (MMF). In secondary forms of MGN, a major part of therapy is the treatment of primary illness. AZA is a drug with proven efficacy in the treatment of SLE and the high incidence of secondary MGN associated with lupus, explains the significant difference in its use in secondary MGN.

Antibodies against the M-type phospholipase A2 receptor (PLA2R) were identified in 2009 and are present in 50-100% in patients with iMGN [11]. Although they were considered pathognomonic for IMGN, later studies showed that they can be found in up to 30% of cases with secondary MGN.

Monotherapy in MGN is insufficiently effective and therefore the treatment is carried out with a combination of immunosuppressive medications. The combination of corticosteroid and an alkylating cytostatic is considered the gold standard in the treatment of MGN [12], although some authors favor other initial treatments, such as corticosteroids and CsA or Rituximab. The most commonly used drug is CYC. Alkylating cytostatics are drugs with well-known toxicity and side effects being directly dependent on the total cumulative dose [13]. Most regimens include oral administration of CYC, whereby high cumulative doses are achieved within a short period of time. When conducting pulse treatment with monthly i.v. administration of high doses of CYC (10-12 mg/kg/monthly), the beneficial effect of treatment is preserved, avoiding the accumulation of high cumulative doses [14, 15], and in the event of relapse of the disease it is possible to carry out subsequent courses of treatment.

The present study shows that the effect on proteinuria reduction and normalization of total protein and albumin levels are comparable in patients receiving low (3500 mg), medium (3500-10,000 mg) and high (over 10,000 mg) doses of CYC. There is no difference in the percentage of patients who have reached complete or incomplete remission and there is no higher relapse rate. In patients, where the initial treatment with CYC was not effective our results show a significant reduction in proteinuria in patients treated with CsA and a corresponding, albeit less pronounced, increase in total protein and albumin. There is no correlation between treatment with CsA and renal function.

Conclusion

Female gender has a more beneficial progression of MGN – lower proteinuria, higher total protein and albumin, and the rate of complete remission is higher. The pulse administration of CYC has an equally beneficial effect in the treatment of MGN compared to oral dosing at significantly lower cumulative doses. Thus, the therapeutic effect is maintained, with a significant reduction in the risk of side effects and adverse reactions. In patients where treatment with corticosteroids and alkylating cytostatic was not effective, adding CsA leads to remission in approximately 60% of the patients.

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