Survival and relapses assessment in patients with Wegener's granulomatosis and predominant renal involvement

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Abstract: Introduction. Wegener's granulomatosis (WG) is a potentially fatal condition with remissions and high relapses rates. **Objectives.** Assessment of survival and relapses in a population based cohort of patients with WG with predominant renal involvement. **Patients and methods.** A prospective cohort study included 60 patients – median age of 42 years – with different dynamics and clinical presentation. Patients were divided into 3 groups (group 1, group 2 and group 3 respectively, and subgroups: 3.1,3.2,.3.3): group 1 – WG patients without renal involvement, group 2 – WG patients with abnormalities in urinary sediment, group 3.1 – WG patients with chronic renal failure, group 3.2 – WG patients with diffuse alveloar hemorrhage (DAH) and rapid progressive glomerulonephritis (RPGN), and group 3.3 – WG patients with RPGN. The clinical analysis has been conducted using the disease extent index (DEI) only and Birmingham Vasculitis Activity Score-Wegener's granulomatosis (BVAS-WG) disease activity questionnaire. Logistic regression analysis and the Wilcoxon test were used. Survival time and death risk were assessed using the Kaplan-Meier estimator and Cox proportional hazard model. **Results.** Eighty-eight percent of patients survived the first year of follow-up since the diagnosis, while 84% of patients remained alive after the second year of observation. Life expectancy was 67.1 ±4.4 months. During the first year of observation 9.8% of patients died, after 2 years death hazard amounted to 3.7% per year, and after 4 years 2.6% per year ($p < 0.05$). Death risk was 1.3-fold higher in group 2 and 3.3-fold higher in group 3 compared to group 1 ($p > 0.05$). Mortality in patients from group 3.1 was 6-fold lower than in patients from group 3.2 ($p < 0.03$) and in group 3.3 was more than 4-fold lower than in patients from group 3.2 ($p < 0.04$). Relapse risk after the first year of follow-up was 20% per year and minimally changed after 3 years of observation, then decreased to 6% after 5 years. Relapse hazard ratio in group 2 was significantly lower in comparison with group 1 (HR1/3.6, $p < 0.04$). **Conclusions.** We found significant differences in survival and relapses in various subpopulations of WG patients.

Key words: death, kidney, relapse, survival, Wegener's granulomatosis

INTRODUCTION

Wegener's granulomatosis (WG) is a primary systemic vasculitis, which ethiopathogenesis still remains unclear and its clinical manifestation is diverse. According to current classification of vasculitis syndromes based on decisions made at the Chapel Hill Consensus Conference in 1994, this nosological entity shall be included in the small vessel inflammation group – the ANCA-positive (*antinuclear cytoplasmatic autoantibodies* – ANCA) vasculitis (*ANCA-associated vasculitis*) [1]. The classic Wegener's triad includes upper and lower respiratory tract involvement and necrotising glomerulonephritis, however, clinical presentation of the disease encompasses a wide range of symptoms resulting from involvement of numerous organs [1,2].

It is a potentially fatal disease. Failure to undertake treatment leads to death in a short time – the mean survival time for untreated patients is estimated at 5 months. The first-year mortality rate is 82%, whereas in the first two years it is 90%, and renal failure is recognised as the leading cause of death (Walton, 1958). In comparison with the limited form, renal involvement considerably deteriorates prognosis. The course of disease is characterised by periods of relapses and remissions. Relapses pose the main and frequent problem of the WG pa-

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tient care. Relapse should be understood as another increase in systemic vasculitis activity, both in respect of inflammation activity and rapid deterioration in organ functions in a patient, who achieved remission upon treatment. In the case of relapse, appropriate diagnostic and therapeutic management has not been determined yet.

The objective of the study was to assess the survival period and relapse risk in a Polish group of the WG patients with predominant renal involvement.

PATIENTS AND METHODS

Characteristics of the study population

The study involved patients hospitalised in the Department of Internal Medicine and Nephrology of Medical University of Warsaw, managed at that time by Professor Kazimierz Ostrowski (the study carried out with his consent). Patient care, diagnostics and treatment were provided by a team managed by Professor Kazimierz A. Wardyn. Persons still followed-up are currently among the patients of the Systemic Vasculitis Clinic of Czerniakowski Hospital and the Department of Internal Medicine and Metabolic Diseases of Medical University of Warsaw. The study was a prospective follow-up including 60 patients: 26 females and 34 males aged 17–73 (45.1 ±14.6), median age 42 (34.5–57.5) with a diagnosis documented since it has been established. Wegener's granulomatosis was diagnosed in the years 1990–2003 based on the following generally accepted criteria: clinical assessment of disease extent, serological assessment (ANCA titres), histopathological examination of biopsy specimens of affected organs and the American Rheumatism Association criteria.

Percentage of patients meeting particular criteria within groups 1, 2, 3.1, 3.2 and 3.3 for inflammatory changes within nose or mouth was: 82%, 74%, 68%, 66% and 52% respectively, for chest x-ray changes: 52%, 58%, 64%, 89% and 71% respectively, for urinary sediment changes: 0%, 72%, 80%, 89% and 94% respectively, and for granulomatous lesions found in a biopsy: 64%, 58%, 62%, 65% and 57% respectively.

The ANCAs were evaluated with a serological test of indirect immunofluorescency. At diagnosis c-ANCA were found in 51 patients and p-ANCAs in 4 patients.

Altogether 21 renal biopsies were performed and their results confirmed diagnoses in 13 cases (pauci-immune lesions); in 8 cases the results of histopathological examination were questionable. For questionable cases, a biopsy of upper respiratory tract (mainly nasal or sinus) wall was performed, which confirmed the diagnosis.

Treatment was being provided upon patients' informed consent. Patients received immunosuppressive therapy (methylprednisolone in pulse dose 500–1000 mg for 3 days, prednisone – 1 mg per kg of body weight per day, orally) and cytotoxic therapy (cyclophosphamide orally or intravenously, 1–4 pulses in total, every 1–4 weeks, adapting the dose to the current GFR value. Haemodialysis and plasmapheresis were also used. The therapy is summarised in fig. 1.

Each patient was assessed in respect of survival time and relapse. The patients were divided into three groups (1, 2 and 3) and group 3 was in turn divided into 3 subgroups: 3.1, 3.2 and 3.3.

Group 1 – patients without renal involvement

This group was made up of 10 patients with a limited form of the disease, where no renal involvement in Wegener's granulomatosis was suggested by a medical history and a physical examination, results of biochemical and imaging tests. Based on medical history data, conclusions concerning chronicity of the disease process were also drawn.

Group 2 – patients with renal involvement manifested by erythrocyturia or proteinuria or red blood cell cast in urinary sediment

This group was made up of 14 patients with a systemic form of the disease, where renal involvement manifested by abnormalities in urine analysis (proteinuria, erythrocyturia, granular and red blond cell casts) was suggested by a medical history and a physical examination, results of biochemical and imaging tests. However, no renal function deterioration was found. Based on medical history data, conclusions concerning chronicity of the disease process were also drawn.

Group 3 – patients with renal involvement and renal failure

Group 3.1 – patients with chronic renal failure

This group was made up of 12 patients with a systemic form of the disease, where renal involvement manifested by abnormalities in urine analysis (proteinuria, erythrocyturia, granular and red blond cell casts) and chronic renal failure resulting from the underlying disease were suggested by a medical history and a physical examination, results of biochemical and imaging tests.

Group 3.2 – patients with rapid progressive glomerulonephritis (RPGN) and diffuse alveolar haemorrhage (DAH)

This group was made up of 8 patients with a systemic form of the rapidly developing disease, where renal involvement manifested by abnormalities in urine analysis (proteinuria, erythrocyturia, granular and red blond cell casts) and rapidly progressing renal failure resulting from the underlying disease, with diffuse alveolar haemorrhage, were suggested by

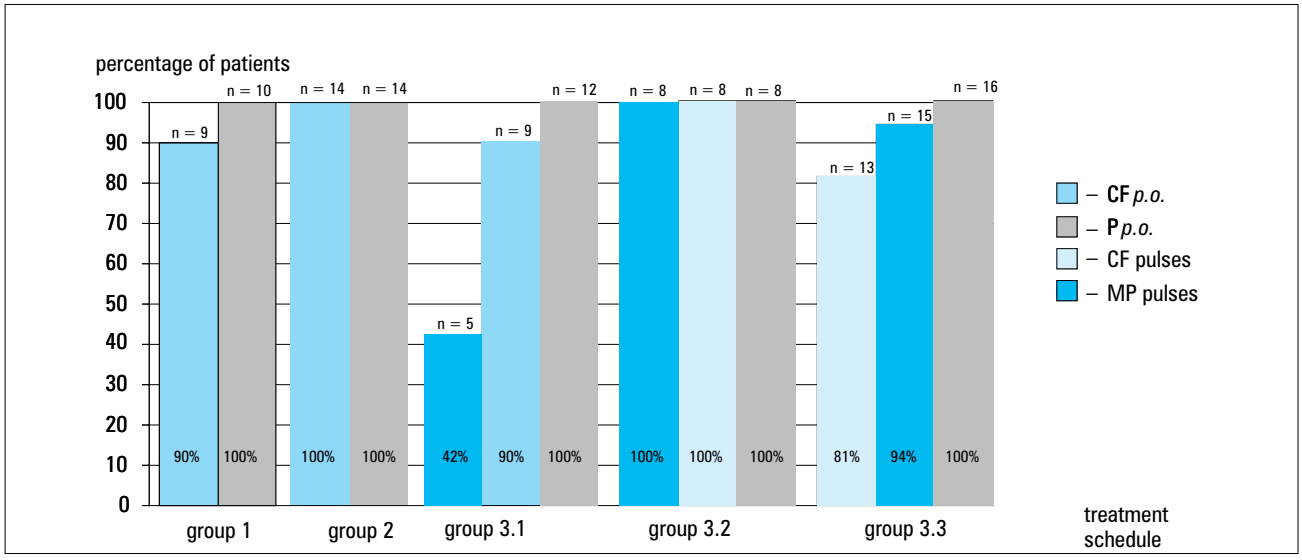

Fig. 1. Percentage of patients undergoing individual treatment schedules. Abbreviations: CF – cyclophosphamide, MP – methylprednisolone, P – prednisone

a medical history and a physical examination, results of biochemical and imaging tests. Based on medical history data, conclusions concerning the speed of the disease progress were also drawn.

Group 3.3 – patients with the RPGN

This group was made up of 16 patients with a systemic form of the rapidly developing disease, where renal involvement manifested by abnormalities in urine analysis (proteinuria, erythrocyturia, granular and red blond cell casts) and rapidly progressing renal failure resulting from the underlying disease were suggested by a medical history and a physical examination, results of biochemical, imaging and histopathological (renal biopsy) tests. Based on medical history data, conclusions concerning rapidity of the disease progress were also drawn.

A relation among the parameters known at diagnosis (duration of symptoms [in months], the possible need for haemodialysis, haemoglobin concentration [g/%], maximum creatinine concentration at diagnosis [mg/dl]) and the risk of death were assessed in all the groups and among them. The mean time until death or relapse, as well as the distribution of organ involvement (Disease Extent Index – DEI), frequency of individual organ involvement, frequency of appearance of clinical symptoms resulting from individual organ involvement, clinical activity score (BVAS index) and immunologic indices of disease activity (ANCA) were also analysed.

Table 1. Age structure, BVAS-WG and DEI scores for analysed groups of Wegener's granulomatosis patients

Group	Age		BVAS-WG		DEI	
	median	(Q1–Q3)	median	(Q1–Q3)	median	(Q1–Q3)
1	43	(39–64)	5.5	(5–7)	7	(7–9)
2	35.5	(31–46)	7.5	(6–11)	9	(9–11)
3.1	47	(38.5–57)	7	(7–8.5)	8	(6–12)
3.2	44.5	(32–66.5)	30	(23–32)	14	(13–15)
3.3	51	(34.5–58)	16	(14.5–19)	11	(9–12)

BVAS-WG – Birmingham Vasculitis Activity Score-Wegener's granulomatosis, DEI – disease extent index

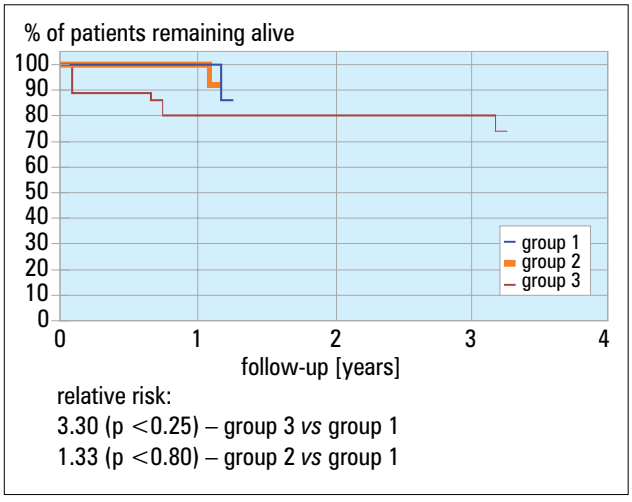

Fig. 2. Survival time in groups 1, 2 and 3

Clinical evaluation

The disease extent index (DEI) and Birmingham Vasculitis Activity Score-Wegener's granulomatosis (BVAS – WG) disease activity questionnaire were applied in clinical analysis.

Statistical analysis

To assess the relation between the parameters known at diagnosis and the risk of death logistic regression analysis was applied; whereas to assess survival time (until death and relapse) the Kaplan-Meier estimator and the Cox proportional hazard model were applied. The relation between qualitative and quantitative variables was assessed by means of the Wilcoxon test.

RESULTS

The analysed group was heterogeneous, including patients with short-lasting, dynamic disease (groups 3.2, 3.3), as well as with long-lasting, chronic course (groups 1, 2, 3). The group was composed of 26 white females and 34 white males aged 17–73 (45.10 ±14.66), median age 42 (34.5–57.5) years.

The median BVAS-WG score was 11 (7–16). The most intense disease activity was observed in patients of groups 3.2 and 3.3, and the least intense in groups 1 and 2. The median DEI score at diagnosis was 10 (5–17) and its highest values were found in groups: 3.2 – median 14 (13–15) and 3.3 – median 11 (9–12), whereas the lowest ones in group 1 – median 7 (7–9). Age structure, the BVAS-WG and DEI scores for individual groups are summarised in table 1.

The first phase of statistical analysis consisted in evaluation of survival time of the WG patients. The follow-up period of all patients was limited to 7 years due to only a few cases of longer follow-up not terminated by death. Table 2 gives percent values of patients surviving subsequent follow-up periods evaluated with the Kaplan-Meier estimator. Eighty-eight percent of patients survived the first year since the diagnosis, after two years, 84% of followed-up patients were left from the original group of 60. After 3, 4, 5, 6 and 7 years of follow-up, the survivors' rate was: 84%, 77%, 77%, 73% and 59% respectively (tab. 2, fig. 1, 2). The mean survival time was 67.1 ±4.4 month. The risk of death was also assessed for subsequent years of follow-up. During the first 2 years since the diagnosis, 9.8% of patients within the first year of follow-up were at risk of death, after 2 years the risk of death in the survivors was 3.7% per year, and 2.6% per year after 4 years. The observed trend for reduction of the risk of death in patients surviving the following years since the diagnosis was statistically significant (p <0.05). The following phase of the analysis consisted in determination of differences in survival rate among groups 1, 2 and 3, and groups 3.1, 3.2 and 3.3. The risk of death in group 2 was found 1.33 times higher, and

Table 2. Survivalof Wegener's granulomatosis patients during a 7-year follow-up inindividual groups

	Follow-up [years]							
	0	1	2	3	4	5	6	7
% of patients remaining alive	100	88	84	84	77	77	73	59
number of patients followed-up at the beginning of a year (n)	60	47	39	39	22	22	19	7
mortality rate [% per year]		9.8		3.7		2.6		
% of patients remaining alive in subsequent years								
group 1	100	100	86					
group 2	100	100	92					
group 3	100	80	80	80	79			
group 3.1	100	100	100	100	80			
group 3.2	100	31						
group 3.3	100	87	87	87	76			

in group 3 – 3.3 times higher than in group 1, however, the difference was not statistically significant. Survival curves of the analysed groups are presented in fig. 3 and table 2. However, significant differences in survival rate were found in patients of groups 3.1, 3.2 and 3.3. In pa- tients of group 3.1, the risk of death was over 6 times lower than in patients of group 3.2 ($p < 0.03$), while in patients of group 3.3 it was over 4 times lower than in patients of group 3.2 ($p < 0.04$). No significant differences were found in survival time between groups 3.1 and 3.3. Survival time percent values for patients of each group are presented in fig. 4 and table 2. The relapse analysis was limited to 43 patients, who survived the first year of follow-up since the diagnosis, while the time to relapse was measured since the first year of the follow-up had been finished. It was concluded that the risk of relapse since the first year of diagnosis was 20% per year and it changed slightly after 3 years of follow-up, to decrease to 6% after 5 years of follow-up (fig. 3). The positive c-ANCA tests were found in 15% of patients with relapse.

Percentage of patients with at least one relapse was 25%, 31%, 42%, 57%, 60% and 60% after 1, 2, 3, 4, 5 and 6 years of follow-up, respectively (tab. 3, fig. 4). The mean time to relapse was 41.4 ±5.0 months. The way, in which a relapse probability changes in relation to a follow-up period, was assessed for each analysed group. It was found that in group 1 the relapse probability in subsequent years was increasing from 42% after the first year of follow-up to 100% after 5 years, while in group 2 and 3 the relapse probability was decreasing (from nearly 10% to 0% after 5 years of follow-up). The significance level defining the differences among the 3 analysed groups in respect of a relapse probability in subsequent years of follow-up was 0.03. The risk of relapse in group 2 was significantly lower than in group 1 (RR 1/3.6, $p < 0.04$), and in group 3 it was 2.9 times lower ($p < 0.03$) than in group 1. The mean time to relapse in groups 1, 2 and 3 was: 20.0 ±6.9 months, 53.3 ±11.0 months and 29.9 ±3.7 months, respectively.

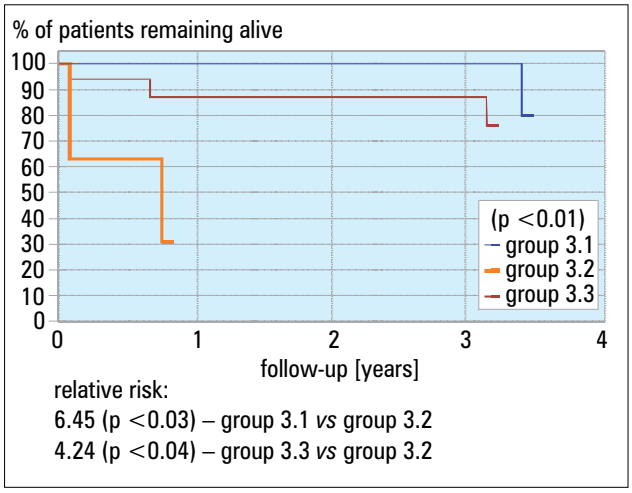

Fig. 3. Survival time in groups 3.1, 3.2 and 3.3

DISCUSSION

Wegener's granulomatosis is a potentially fatal disease, whose recognition and differential diagnosis are complex issues. In differential diagnosis there shall be considered other potential conditions with simultaneous renal involvement, like systemic lupus erythematosus, Churg-Strauss syndrome, microscopic polyangiitis (MPA), Schönlein-Henoch purpura and cryoglobulinaemia.

Failure to undertake treatment leads to death in a short time and the mean survival time for untreated patients is estimated at 5 months. The first-year mortality rate is 82%, whereas in the first two years it is 90%, and renal failure is recognised as the leading cause of death [1,3]. The first medications used in the WG treatment were glycocorticosteroids, which extended survival time by only 12.5 months, however, mortality resulting from infections increased and disease control was not achieved (Hollander, Manning, 1967). In a NIH (National Institutes of Health) study, 96% of patients treated with monotherapy with glycocorticosteroids showed no remission, while 45 patients with renal failure showed no renal function improvement. An alkylating agent (mustard acid) was used for the first time by Fahey in the treatment of a 38-year-old male with the WG in 1954 and clinical improvement was observed afterwards. However, there is no data concerning the survival time of the patient. Since then, an appropriate, effective WG treatment schedule has been sought, with numerous attempts to combine several cytotoxic agents with each other or with glycocorticosteroids. In 1972 Fauci and Wolff revolutionised treatment of the disease introducing cyclophosphamide combined with glycocorticosteroids, which significantly extended survival time and reduced mortality in the WG [4].

The first attempts of the WG treatment in Poland also ended in failure [5-7]. They consisted in the use of cortisone (*i.v.*), prednisolone (*p.o.*) and radiotherapy. In Poland, cyclophosphamide was first used in 11 out of 12 patients of the Department of Otolaryngology of Medical Centre of Postgraduate Education [8]. In the years 1971–1980, 10 out of the 54 WG patients were provided with cytotoxic treatment, as reported by Wiatr et al. [9]. Nine of them survived at least one year. In the years 1981–1990, cytotoxic agents were used in 20 out of 22 patients. There is data on survival time of 9 patients, of whom 8 survived 3–12.5 years. The efficacy of cyclophosphamide treatment was spectacular, poor results were reported only for cases of extremely advanced disease. Due to high mortality and therapeutic difficulties, another effort was made to assess the clinical course of the disease and treatment efficacy. With reference to studies by Wiatr (n = 54) and Dąbrowski (n = 18), it is the largest group (n = 60) of Polish WG patients analysed to date [9, 10]. Particular attention was paid to the patients' survival time. The follow-up period of all patients was limited to 7 years due to only a few cases of longer follow-up not terminated by death. 88% of patients survived the first

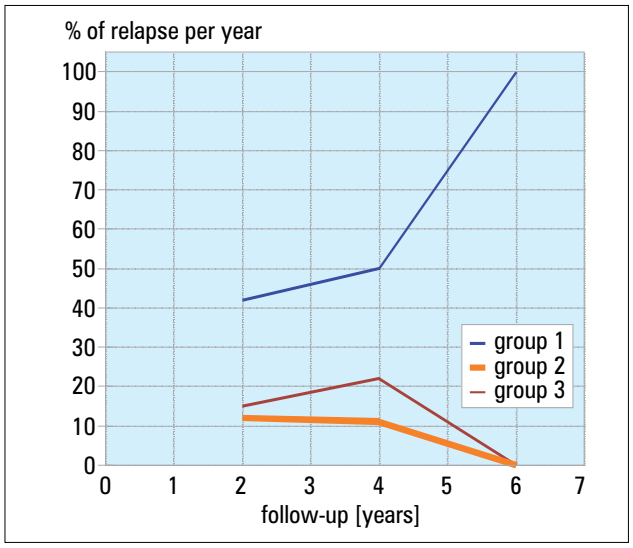

Fig. 4. Risk of Wegener's granulomatosis relapse during 7-year follow-up

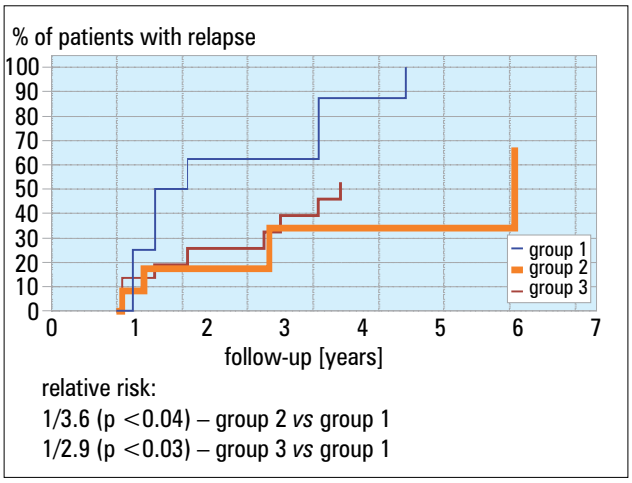

Fig. 5. Wegener's granulomatosis relapse during 7-year follow-up

year since the diagnosis, after two years, 84% of followed-up patients were left from the original group of 60. After 3, 4, 5, 6 and 7 years of follow-up, the survivors' rate was: 84%, 77%, 77%, 73% and 59% respectively. The mean survival time was 67.1 ±4.4 month. Percentage of patients, who survived the first year of disease, seems to prove severity of the disease course (as compared with the analogous percentage in a study by Reinhold-Keller et al.) [11]. To date, there has been no Polish study providing the assessment of precise survival time of the WG patients, including survival of the first year of disease. Information about the survival time of patients followed-up long enough can be found only in the study by Wiatr et al. The study included 54 WG patients. In the years 1959–1970, 15 patients were under follow-up; 5 out of 13 patients followed-up long enough survived at least 1 year.

In the years 1971–1980, 17 patients were followed-up. 9 out of 14 patients followed-up long enough survived at least 1 year. In the years 1981–1990, 22 patients were followed-up. In this group the survival time of 9 patients was reported; 8 of them survived 3–12.5 years [9]. Patients' survival time was not indicated by Hoffman in his study [12]. The aforementioned study by Reinhold-Keller reports the mean survival time of 21.7 years. 99% of all patients survived the first year of disease, 97% of patients survived 2 years and 88% – 10 years. Patients included in the study seemed to show no "severe" systemic symptoms. The total mortality rate in a study by Koldingsnes was 23.2% (13 patients died) [13]. 93% of patients survived the first year since the diagnosis, after 5 years, 79% of followed-up patients were left from the original group of 58, after 10 years of follow-up, 75% of patients remained alive. Four patients (7.1%) died within the first month of treatment; systemic multi-organ disease was found in all patients, and the patients' BVAS score exceeded 31.

According to a study by Palvone et al., advanced age and kidney, liver and the CNS involvement were associated with an

Table 3. Wegener's granulomatosis relapse events and relapse risk within a 7-year follow-up since the diagnosis

Diagnosis	Start of follow up	Follow-up [years]						
		0	1	2	3	4	5	6	7
accumulated percentage of patients with relapse		0	25	31	42	57	60	60	
number of patients still followed-up	n = 60	n = 43	n = 28	n = 22	n = 16	n = 12	n = 11	n = 11	
risk of relapse			19.4		22.6			5.9	
group 1	n = 10	0% per 1 year	42% per 1 year		50% per 1 year		100% per 1 year		
group 2	n = 14	0% per 1 year	12% per 1 year		11% per 1 year		0% per 1 year		
group 3	n = 36	0% per 1 year	15% per 1 year		22% per 1 year		0% per 1 year		

increased risk of death. The values were as follows: HR 4.05, 95% CI: 1.229–12.73, p = 0.017 for age, HR 5.16, 95% CI: 1.16–22.95, p = 0.0031 for renal involvement, HR 4.12, 95% CI: 1.44–12.84, p = 0.009 for liver involvement and HR 4.49, 95% CI: 0.97–20.82, p = 0.055 for the CNS involvement [14]. Similar trends were observed by Khan et al. [15].

In a study by Rihova et al., which included 61 patients, the estimated patient survival at 5 and 10 years was 78.3 and 62.2%, respectively (fig. 3) and was significantly lower in patients >60 years of age at diagnosis in comparison with patients <60 years of age (p = 0.029). Similar results were obtained in patients over and under 50 years of age (p = 0.04). The estimated patient survival did not depend on sex, proteinuria, the CRP and haemoglobin concentration. A shorter survival time was reported in patients, who required haemodialysis at diagnosis as compared with patients, who did not undergo dialysis (p = 0.0380) [16].

Relapses pose the main and frequent problem of the WG patient care. Relapse should be understood as another increase in systemic vasculitis activity, both in respect of inflammation activity and rapid deterioration in organ functions in a patient, who achieved remission upon treatment. In the case of relapse, appropriate diagnostic and therapeutic management has not been determined yet.

Relapse rate in the AAV patients ranges from 25% to 80% and depends on individual features, the duration of symptoms prior to treatment, as well as the treatment protocol. Among many analysed relapse risk factors, the following seem to be the most relevant and the most reliable: high ANCA titres despite treatment (no serological negativisation), chronic infections – colonisation of nasal mucosa with *Staphylococcus aureus* and upper respiratory tract involvement [17-22]. Opposite relations were observed in the study by Pavone et al. [14].

Relapse analysis was limited to 43 patients, who survived the first year of follow-up since the diagnosis, and time to relapse was measured since the end of a one-year follow-up. It was concluded that the risk of relapse since the first year of diagnosis was 20% per year and it changed slightly after 3 years of follow-up, to decrease to 6% after 5 years of follow-up. Percentage of patients with at least one relapse was 25%, 31%, 42%, 57%, 60% and 60% after 1, 2, 3, 4, 5 and 6 years of follow-up, respectively. The mean time to relapse was 41.4 ±5.0 months. The way, in which a relapse probability changes in relation to a follow-up period, was assessed for each analysed group. It was found that in group 1 the relapse probability in subsequent years was increasing from 42% after the first year of follow-up to 100% after 5 years, while in group 2 and 3 the relapse probability was decreasing (from nearly 10% to 0% after 5 years of follow-up). The significance level defining the differences among the 3 analysed groups in respect of a relapse probability in subsequent years of follow-up was 0.03. The risk of relapse in group 2 was significantly lower than in group 1 (RR 1/3.6, p <0.04), and in group 3 it was 2.9 times lower (p <0.03) than in group 1. The mean time to relapse in groups 1, 2 and 3 was: 20.0 ±6.9 months, 53.3 ±11.0 months and 29.9 ±3.7 months, respectively.

Polish literature does not provide such precise information concerning relapse in assessed groups. Only a study by Dąbrowski reported a 50% relapse rate (in 9 out of 18 patients) [10]. At the end of treatment, the following sites of relapse were reported: lungs – 4 cases, kidney – 1 case, eyeball – 2 cases and nervous system – 4 cases. According to Hogan, upper respiratory tract involvement (as a predominant location) is a relapse risk factor, as well as the persisting ANCA activity. It was observed in 90% of patients of group 1, i.e. a group at the highest risk of relapse. In the study by Hoffman, relapse upon remission was reported in 49% of patients [12].

In the study by Reinhold-Keller, relapse upon remission was observed in 99 patients (65%) [11]. The relapse rate was increasing along with follow-up duration: 13 out of 34 patients (38%) were followed-up less than 5 years, while 86 out of 121 more than 5 years. In this group, like in the study in question, the high ANCA titres were reported in all patients with relapse. In the study by Pavone et al., the risk of relapse within the first and second year after remission was 16% and 26%, respectively. The GI involvement was related to the increased risk of relapse [14].

In the study by Rihowa, relapse was recorded in 44.7% of patients. The median disease-free interval was 58 (0–138) months, whereas the median renal disease-free interval was 62.5 (0–138) months [16]. Relapses happened mainly, when patients have no longer been undergoing immunosuppressive therapy (in 81.5% of patients); in 4 patients treated with azathioprine (14.8%) and in 1 patient treated with cyclophosphamide (3.7%). Each relapse event was associated with the positive ANCA test results. During remission, the ANCA tests were positive in only 2 patients, who did not relapse. The relapse rate was higher in patients with a disease associated with c-ANCA, and not with p-ANCA, although the difference was at the verge of statistical significance (p = 0.059) [16].

The conclusions drawn were as follows:

1) there exist fundamental differences in the survival time and relapse rate among individual analysed groups, depending on:
   a) disease dynamics
   b) disease activity
   c) lesion sites
   d) disease duration
2) survival time in the WG patients is determined by a number of involved systems and a level of individual organ damage, particularly by renal and respiratory tract involvement. The involvement of those systems requires renal replacement therapy or leads to acute respiratory failure.
3) the highest risk of death was reported in patients with coexisting diffuse alveolar haemorrhage (DAH) and rapid progressive glomerulonephritis (RPGN)
4) isolated involvement of upper respiratory tract in Wegener's granulomatosis is associated with the highest risk of relapse.

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