Respiratory involvement in antineutrophil cytoplasmic antibody-associated vasculitides: a retrospective study based on the POLVAS registry

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Abstract

Objective

The study aimed to characterise the Polish population of (ANCA)-associated vasculitides (AAV) with respiratory involvement (RI), in comparison to the subgroup without lung manifestations and the other cohorts.

Methods

Retrospective analysis of the Polish population of AAV with RI was conducted, based on data from the POLVAS registry. Standard descriptive statistics, $\chi 2$ test, and Mann-Whitney U test were used to perform comparisons.

Results

Among 461 cases qualified to this study, there were 316 cases with RI (68.5%), 206 with granulomatosis with polyangiitis (GPA) (65.2%), 80 with eosinophilic granulomatosis with polyangiitis (EGPA) (25.3%) and 30 with microscopic polyangiitis (MPA) (9.5%). Proportion of RI in GPA, MPA, and EGPA accounted for 67.8%; 40.0%; 97.6%, respectively. The number of relapses was higher in the RI group (median 1.0 vs. 0.0; p=0.01). In the subgroup of combined GPA and MPA with RI, the trends toward higher proportion of deaths (11.7% vs. 5.7%; p=0.07), relapses requiring hospitalisation (52.2% vs. 42.4%, p=0.07) and relapses requiring admission to the intensive care unit (5.6% vs. 1.4%, p=0.09) were observed, median maximal concentration of CRP was higher (46 vs. 25 mg/l; p=0.01) and more aggressive treatment was administered.

Conclusion

Prevalence of RI in the Polish population of AAV is similar to the values reported in the literature, however, the proportion observed in GPA is closer to those presented in Asian than Western European cohorts. RI seems to be associated with a more severe course of disease and its presence prompts more aggressive treatment.

Key words

ANCA, vasculitis, AAV, respiratory involvement, lung involvement

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Introduction

Antineutrophil cytoplasmic antibody (ANCA)-associated vasculitides (AAV) is a group of rare (1), autoimmune diseases of unknown aetiology and varied clinical image, which may present as a systemic disease with multiorgan involvement. The group of AAV consists of three distinct entities: granulomatosis with polyangiitis (GPA), microscopic polyangiitis (MPA) and eosinophilic granulomatosis with polyangiitis (EGPA) (2). The diagnostic process leading to establishing the diagnosis of AAV is complex. Usually, it requires a combination of clinical data, laboratory tests, imaging and histopathologic analysis of tissues from a biopsy.

Respiratory system involvement is one of the frequent manifestations, which in some cases is the most severe one, significantly influencing the outcome (3-5). Pulmonary manifestations in AAV are diverse and depend on the particular entity and ANCA pattern. The most common types of lung involvement in GPA are nodules with or without cavities, infiltrates and focal consolidations. In contrast, diffuse alveolar haemorrhage (DAH) and interstitial lung disease (ILD) are most typical in MPA. On the other hand, asthma is present in over 95% of EGPA cases, while ground-glass opacities in lung imaging are the second most prevalent respiratory manifestation (3-8). The Consortium of the Polish Vasculitis Registry (POLVAS) is a multicentre initiative designed to collect data, regarding prevalence, clinical features, treatment and outcomes of vasculitides among the Polish population. More detailed information on the POLVAS project is presented separately (9-12).

Being aware of the respiratory involvement significance in the course of AAV (8, 11, 13-16), we decided to detail the Polish population of AAV patients with respiratory involvement, based on data gathered in the POLVAS retrospective database.

Materials and methods

Six hundred and twenty-five cases of AAV diagnosed from 1990 to 2016 and remaining under the care of POLVAS affiliated centres were included in the retrospective part of the POLVAS database. The retrospective analysis was conducted and relevant data were collected using electronic questionnaires. All cases of AAV available in the documentation gathered in the POLVAS affiliated centres were included. Cases had to satisfy the American College of Rheumatology (ACR) classification criteria and/or the 2012 Revised International Chapel Hill Consensus criteria (2, 17).

Respiratory involvement in POLVAS database was defined as the occurrence of at least one symptom, sign, result of imaging test or condition attributable to AAV from the list included in POLVAS questionnaires. The list is presented in Table I. The status of respiratory involvement was unknown in 5 cases included in the POLVAS database, 620 cases were therefore qualified for further analysis. From the group encompassing the cases with respiratory involvement according to POLVAS definition, we selected only those with radiologically confirmed lesions. This subgroup was compared to the subgroup without respiratory involvement.

The study was carried out under the ethical principles of The Declaration of Helsinki developed by the World Medical Association. The study protocol was approved by the Jagiellonian University Bioethics Committee (Krakow, Poland) No. 122/6120/25/2016. All POLVAS participating centres acquired local ethics committee approval.

Standard descriptive statistics were used. The normal distribution of variables was checked by the Shapiro-Wilk test. To compare the studied groups $\chi 2$ test (with Yates correction if needed) for dichotomous variables and Mann-Whitney U-test for continuous variables were used. The p-value <0.05 was assumed as statistically significant, modified with Bonferroni correction when multiple comparisons were performed. Calculations were conducted with StatSoft Statistica 13 software (StatSoft®, Tulsa, OK, USA).

Results

Four hundred and seventy-five cases presented with respiratory involvement, according to POLVAS definition. From this group, 316 individuals (66.5%) had

radiological confirmation of pulmonary abnormalities (RI group). They were included into further analysis and compared to the group without respiratory involvement (non-RI group), which involved 145 cases. After exclusion of the cases with pulmonary abnormalities but without proving on imaging tests, the prevalence of respiratory involvement in the selected group amounted to 68.5% (316/461).

Patients from the non-RI group were older than those form the RI group at the time of diagnosis (median values: 53 *vs*. 51 years). The prevalence of GPA, MPA and EGPA in the RI group amounted to 65.2%, 9.5% and 25.3%, respectively. Respiratory involvement with radiological confirmation was present in 97.6% *vs*. 67.8% *vs*. 40.0% cases of EGPA, GPA and MPA cases, respectively. The differences were statistically significant. The details regarding the comparison of particular AAV presence between RI and non-RI groups are included in Table II.

Most of the RI patients had additional organ involvement (97.8%). In both groups the most affected organs were kidneys (in the MPA subgroup 90.0% *vs*. 97.7% in the RI and non-RI groups, respectively), ear/nose/throat and musculoskeletal system. In the RI group constitutional symptoms, ear/nose/throat (ENT), cardiovascular, gastrointestinal, central and peripheral nervous systems involvement were present significantly more frequently than in the non-RI patients (89.8% *vs*. 80.6%, 74.3% *vs*. 60.0%, 23.5% *vs*. 9.0%; 16.6% *vs*. 7.6%; 10.6% *vs*. 4.1%; 28.8% *vs*. 15.9%, respectively).

There was no difference in mortality between the RI and non-RI groups, however raw proportion of deaths was higher in the RI group (9.0% *vs*. 5.8%). The overall number of relapses were significantly higher in the RI group (median=1 *vs*. median=0, respectively). The percentage of cases, requiring hospitalisation or admission to the intensive care unit (ICU) were also higher in the RI group, however they did not reach statistical significance. Patients from the non-RI group had slightly higher maximal creatinine level.

Table I. Symptoms, signs, conditions and results of additional tests attributable to respiratory involvement included in the POLVAS questionnaire.

Symptoms and signs	Dyspnoea Dry cough Wet cough with purulent sputum Haemoptysis Wheezing Pleural pain Other symptoms/signs related to respiratory system
Results of imagining tests	Lung fibrosis Nodules or cavities in lungs Lung infiltration Diffuse alveolar haemorrhage Pleural effusion
Other clinical conditions associated with respiratory involvement	Respiratory disorders requiring oxygen therapy Respiratory failure requiring intubation

Table II. Comparison of chosen parameters between the RI and non- RI groups.

	RI group	Non-RI group	*p*-value
General data			
GPA	206/316; 65.2%	98/145; 67.6%	0.61
MPA	30/316; 9.5%	45/145; 31.0%	**<0.01**
EGPA	80/316; 25.3%	2/145; 1.4%	**<0.01***
Men	149/316; 47.2%	57/145; 39.3%	**0.12**
Age at the time of diagnosis (years)	51.0 (36.0-60.0)	53.0 (40.0-65.0)	0.02
Time of observation (months)	57.0 (24.0-98.0)	41.0 (16.0-103.0)	0.13
Smoking (current or past)	74/207; 35.7%	38/97; 39.2%	0.56
Symptoms and signs			
Constitutional symptoms	283/315; 89.8%	116/144; 80.6%	**0.01**
Musculoskeletal system	185/310; 59.7%	78/145; 53.8%	0.24
Skin	121/314; 38.5%	46/143; 32.2%	0.19
Eye/ophthalmological manifestations	65/312; 20.8%	31/143; 21.7%	0.84
Ear/nose/throat (ENT)	234/315; 74.3%	87/145; 60.0%	**<0.01**
Cardiovascular system	74/315; 23.5%	13/144; 9.0%	**<0.01**
Gastrointestinal system	52/314; 16.6%	11/145; 7.6%	**0.01**
Kidneys	175/315; 55.6%	88/142; 62.0%	0.20
Genitourinary system	7/315; 2.2%	1/144; 0.7%	0.44*
Central nervous system (CNS)	33/312; 10.6%	6/145: 4.1%	**0.02**
Peripheral nervous system	218/306; 28.8%	23/145; 15.9%	**<0.01**
Deaths and relapses			
Deaths	28/310; 9.0%	8/137; 5.8%	0.25
Total number of relapses	1.0 (0.0-2.0)	0.0 (0.0-1.0)	**0.01**
Relapses requiring hospitalisation (at least one)	135/277; 48.7%	59/141; 41.8%	0.18
Relapses requiring ICU stay	14/276; 5.1%	2/140; 1.4%	0.12
Laboratory tests			
cANCA presence	170/268; 63.4%	72/121; 59.5%	0.46
pANCA presence	51/268; 19.0%	42/121; 34.7%	**<0.01**
ANCA absence	47/268; 17.5%	7/121; 5.8%	**<0.01**
anti-PR3	168/254; 66.1%	80/130; 61.5%	0.2553
anti-MPO	52/252; 20.6%	42/127; 33.1%	**0.01**
Eosinophilia	84/275; 30.5%	5/125; 4.0%	**<0.01**
Maximal CRP serum concentration (mg/l); &	38.0 (12.0-90.3)	25.1 (6.6-75.7)	0.06
Maximal creatinine concentration (mg/dl)	1.0 (1.0-2.1)	1.3 (1.0-4.6)	**0.02**

Data are presented as proportions and percentage or median and interquartile range, as appropriate. The proportions included in the columns described as RI group and non-RI group are the proportions of cases with the relevant feature to all cases with or without RI, respectively.
*Yates correction used; &at the time of diagnosis.
Statistically significant values are in bold.
PR3: proteinase 3; MPO: myeloperoxidase.

Table III. Comparison of treatment administered in the RI and the non-RI group.

	RI group	Non-RI group	*p*-value
Remission induction treatment			
GCs	310/315; 98.4%	131/144; 91.0%	**<0.01**
GCs without any other immunosuppressive drug	34/315; 10.8%	22/144; 15.3%	0.17
GCs pulses used (at least 1)	185/237; 78.1%	87/129; 67.4%	**0.03**
CYC	252/315: 80.0%	107/144; 74.3%	0.17
RTX	24/315: 7.6%	9/144; 6.3%	0.630
MTX	18/315; 5.7%	11/144; 7.6%	0.43
AZA	21/315; 6.7%	2/144; 1.4%	**0.03***
MMF	2/315: 0.6%	1/144; 0.7%	0.58*
IVIG	21/315: 6.7%	3/144; 2.1%	0.07
Plasmaphereses	29/313; 9.3%	11/139; 7.9%	0.64
Haemodialysis (permanently and temporarily)	48/312; 15.4%	37/140; 26.4%	**0.01**
Haemodialysis (permanently)	27/312; 8.7%	28/140; 20.0%	**<0.01**
Maintenance treatment			
GCs	223/265: 84.2%	115/139; 82.7%	0.71
AZA	118/265; 44.5%	42/139; 30.2%	**0.01**
MTX	73/265: 27.5%	35/139; 25.2%	0.61
MMF	48/265; 18.1%	19/139; 13.7%	0.25
CYC	32/265; 12.1%	11/139; 7.9%	0.20
CYA	15/265; 5.7%	5/139; 3.6%	0.36
RTX	3/265; 1.1%	2/139; 1.4%	0.83*

*Yates correction used. Statistically significant values are in bold.
CYC: cyclophosphamide; RTX: rituximab; MTX: methotrexate; AZA: azathioprine; MMF: mycophenolate; IVIG: intravenous immunoglobulins; CYA: cyclosporine.

Detailed information on the laboratory differences between the RI and non-RI groups are shown in Table II.

Interestingly, glucocorticosteroids (GCs) in the induction remission phase and GCs pulses were used significantly more frequently in the RI group (98.4% *vs*. 91.0% and 78.1% *vs*. 67.4%, respectively). Additionally, azathioprine was administered more frequently in the RI group in both remission induction and maintenance treatment (6.7% *vs*. 1.4% and 44.5% *vs*. 30.4%, respectively), comparing to the non-RI patients. On the other hand, patients from the non-RI group were haemodialysed more frequently than those from RI group. The details are presented in Table III.

We also analysed respiratory involvement in the subgroups – GPA, MPA and a combined subgroup of GPA and MPA individuals (GPA-MPA; EGPA cases excluded). In the latter subgroup, constitutional symptoms, musculoskeletal, ENT and CNS involvement were more prevalent in RI group, as compared to the non-RI group. Moreover, those subjects were characterised by a significantly elevated maximal CRP concentration (46 *vs*. 25 mg/l) and the more severe course of the disease, requiring relevantly more frequent use of GCs, GCs pulses, cyclophosphamide, and IVIG as well as rarer use of GCs as the only medicament during the remission induction treatment. The proportions of relapses requiring hospitalisation, relapses requiring ICU stay and deaths were also higher in the RI group, nonetheless did not reach statistical significance (52.2% *vs*. 42.4%, $p= 0.07$; 5.6% *vs*. 1.4%, $p=0.09$; 11.7% *vs*. 5.7%; $p=0.07$; respectively). On the other hand, permanent need for haemodialysis was observed more frequently in the non-RI group.

In the GPA subgroup the results were similar to these observed in the combined GPA-MPA subgroup, as the cases with GPA considerably prevailed in that cohort. Interestingly, all patients in MPA RI group were treated with GCs and cyclophosphamide during remission induction phase. In comparison to the MPA non-RI group, cyclophosphamide use as well as using GCs along with another immunosuppressive drug (not as an only medicament) during remission induction treatment were significantly more prevalent.

The details are presented in Table IV, only statistically significant differences are shown.

To better describe POLVAS cohort, we also performed analyses, considering all cases, meeting the POLVAS criteria of respiratory involvement (not only those with radiological confirmation). The data are included in the supplementary material.

Discussion

In the present study, in a large group of more than 450 cases, we have demonstrated that the prevalence of respiratory involvement in AAV is high (68.5%). Presence of pulmonary abnormalities was particularly widespread in our EGPA cohort (97.6%), as it usually reaches 90-91% (asthma excluded), according to the literature data (6, 7, 18). The percentage of respiratory involvement cases was higher in GPA than in MPA, which is commonly reported in other studies (7, 19, 20). The overall rate of respiratory involvement in GPA and MPA subgroups was comparable to the other cohorts. Of note, the proportion of cases with RI in GPA subgroup was more similar to those observed in Asian cohorts than in Western Europe (RI rates: GPA in Europe, range: 40.6%-67.0% *vs*. GPA in Asia, range: 67.6-69.5%) (14, 19-24). That may be the proper distinction between Central and Western European populations of GPA; however, it could also result from the differences in definitions or study protocols used in various studies (25).

Slight male predominance was noticed in the GPA and GPA-MPA RI subgroups with significant higher proportion of men, when compared to non-RI GPA and GPA-MPA subgroups. The data, regarding the sex ratio in the available literature are equivocal (4, 5, 8).

Pulmonary involvement was accompanied by other organ manifestations in the majority of cases. In particular, all individuals with MPA had at least one more organ affected, including kidneys in 90% of cases, similarly to the other reports (26). Cardiovascular, gastrointestinal, and peripheral nervous system involvement were observed more frequently in the RI group, mainly due to EGPA prevalence, for which these

Table IV. Differences between the RI and the non-RI group in defined subgroups.

	RI group		Non-RI group		*p*-value
GPA subgroup					
Men	106/206	51.5%	37/98	37.8%	0.03
Constitutional symptoms	186/205	90.7%	77/97	79.4%	0.01
Renal involvement	126/206	61.2%	45/96	46.9%	0.02
Maximal creatinine concentration (mg/dl); median	1.03	(1.0-2.78)	1.00	(0.88-2.2)	0.02
Maximal CRP concentration (mg/l); median[&]	45.5	(13.0-103.5)	22.0	(5.0-75.7)	0.02
Total GCs use[#]	200/205	97.6%	86/97	88.7%	<0.01
GCs without any other immunosuppressive drug[#]	7/205	3.4%	12/97	12.4%	<0.01
CYC use[#]	186/205	90.7%	74/97	76.3%	<0.01
GCs pulses use (at least one)	149/179	83.2%	57/86	66.3%	<0.01
MTX use[#]	9/205	4.4%	10/97	10.3%	<0.05
MPA subgroup					
GCs without any other immunosuppressive drug[#]	0/30	0.0%	10/45	22.2%	0.02[*]
CYC use[#]	30/30	100.0%	33/45	73.3%	0.01
GPA-MPA subgroup					
Men	123/236	52.1%	56/143	39.2%	0.01
MPA diagnosis	30/236	12.7%	45/143	31.5%	<0.01
Constitutional symptoms	212/235	90.2%	114/142	80.3%	0.01
Musculoskeletal system	150/233	64.4%	77/143	53.8%	0.04
Ear/nose/throat (ENT)	166/235	70.6%	87/143	60.8%	<0.05
Central nervous system involvement	27/232	11.6%	6/143	4.2%	0.01
Maximal CRP concentration (mg/l); median[&]	46.0	(14.0-105.0)	25.0	(6.6-75.1)	0.01
c ANCA presence	161/208	77.4%	72/119	60.5%	<0.01
p ANCA presence	38/208	18.3%	40/119	33.6%	<0.01
anti-PR3	164/218	75.2%	80/129	62.0%	0.01
anti-MPO	38/216	17.6%	41/126	32.5%	<0.01
Total GCs use[#]	230/235	97.9%	129/142	90.8%	<0.01
GCs without any other immunosuppressive drug[#]	8/235	3.4%	22/142	15.5%	<0.01
CYC use[#]	216/235	91.9%	107/142	75.4%	<0.01
IVIG use[#]	19/235	8.1%	3/142	2.1%	0.03
GCs pulses use (at least one)	175/208	84.1%	86/127	67.7%	<0.01
AZA use[$]	100/233	42.9%	42/137	30.7%	0.02
Haemodialysis (permanently)	27/232	11.6%	28/138	20.3%	0.02

[*]Yates correction used. [&]At the time of diagnosis. [#]In remission induction treatment. [$]In maintenance treatment.

manifestations are more characteristic than for the other AAV (6, 19). However, constitutional symptoms, ENT and CNS involvement prevailed both in the whole RI group and GPA-MPA subgroup. There was also a significant predominance of renal involvement in the GPA RI group, comparing to the GPA non-RI group, which might indicate the subset of more severe GPA presentation.

We found a higher rate of relapses in the all AAV RI group. However, the overall rate did not differ after the exclusion of EGPA cases, suggesting a milder course of EGPA exacerbations, which perhaps were usually asthma control worsening. Due to some specific features, like eosinophilic inflammation, association with asthma, and unique options for treatment, EGPA is considered to be a prominently different entity from the other AAV. Based on this knowledge we created and analysed the combined GPA-MPA subgroup, which approach is supported by literature data (27-29).

The analysis of GPA-MPA subgroup did not reveal the significant difference of death incidence, relapses requiring hospitalisation and relapses requiring ICU stay in the RI group, however there was a trend towards higher proportions of these parameters, comparing to the non-RI group Moreover, they reach statistical significance, when analysing all the cases fulfilling POLVAS definition of respiratory involvement (data shown in supplement). Additionally, CRP, which is one of the markers of active disease in AAV (30), was elevated (median maximal concentration) in the GPA-MPA RI group, comparing to the non-RI groups. Considerably more frequent use of GCs, GCs pulses, cyclophosphamide, IVIG and rarer administration of GCs without any other immunosuppressive drugs in the remission induction phase in GPA-MPA RI group (GCs and GCs pulses use also significantly more prevalent in all AAV RI group), comparing to non-RI group indicate more intense treatment regimen in cases with respiratory involvement. In MPA RI subgroup all cases were treated with GCs and cyclophosphamide, whereas some patients in the MPA non-RI group were administered only GCs for remission induction treatment. Together, these findings may suggest a more severe course of the disease and poorer outcome associated with respiratory involvement. Although respiratory involvement is not mentioned as the main factor influencing relapse rate or long-term outcome by recent reviews (1), particular manifestations, such as DAH or ILD with pulmonary fibrosis, are proved to be associated with poorer prognosis (4, 8, 15, 16, 31, 32). The occurrence of pulmonary damage is also a frequent reason for ICU admission or comorbidity of importance in patients treated in ICU, which suggests its association with more severe AAV exacerbation (33, 34). However, we did not obtain a statistically significant difference regarding mortality in the whole cohort as well as in the subgroups.

Nonetheless, taking into consideration that DAH might be the first manifestation of AAV with high mortality (13, 35, 36), as well as its high prevalence in AAV cases treated in the ICU units (32, 33), part of the most severe cases may be admitted to ICU wards and die without establishing a full diagnosis. It may result in the underestimation of deaths due to acute pulmonary manifestations in AAV.

On the other hand, we found higher median maximal creatinine concentration and more frequent need for haemodialysis in the all AAV non-RI subgroup. Permanent haemodialysis was also required more often in GPA-MPA non-RI subgroup. Conversely, renal involvement and higher maximal creatinine

concentration were observed in GPA RI subgroup. These findings seem to be associated with higher prevalence of MPA in non-RI groups, which is associated with frequent renal involvement and its severe course (19, 20, 26, 37).

Our study has several significant limitations. First of all, it is based on retrospective data, which may affect the possibility of forming precise conclusions and comparing results with prospective cohorts. Secondly, the definition of respiratory involvement used in the POLVAS database is broad; thus, its interpretation does not differentiate between distinct kinds of pulmonary manifestations. Therefore, it might not be possible to determine the type of respiratory involvement. It may lead to major misconceptions as the significance of asymptomatic pulmonary nodules and DAH is considerably different. To partially overcome this limitation, we selected the subgroup with radiologically confirmed disease. Unfortunately, there is no information on the type of performed imaging test, which may limit interpretation, as the sensitivity of X-ray and computed tomography is different. Due to the inclusion of only the cases with radiological confirmation, we had to exclude from the analysis 154 cases, which may result in the bias. Nevertheless, even after reducing the strength of the cohort, we were still able to involve over 450 cases in the study, which constitutes high number of AAV cases.

Therefore, we believe that the number of cases included in the study, as well as the similarity of the main characteristics of this group to the other cohorts, makes this report reliable and valuable. Creation of the POLVAS registry by the collaboration of 9 prominent medical centres in Poland, which is to date the largest database of AAV cases in Poland, enabled to characterise Polish population of AAV. The ongoing prospective part of POLVAS project holds the promise of obtaining more detailed results.

The involvement of the respiratory system occurred in nearly 70% of the studied group. It was similar to the reports from the other countries, however, the proportion observed in GPA is closer to those presented in Asian than Western European cohorts. Respiratory involvement seemed to be associated with a more severe disease course in GPA and MPA and its presence prompted more aggressive treatment.

References

1. BERTI A, DEJACO C: Update on the epidemiology, risk factors, and outcomes of systemic vasculitides. *Best Pract Res Clin Rheumatol* 2018; 32: 271-94.
2. JENNETTE JC, FALK RJ, BACON PA *et al*.: 2012 revised International Chapel Hill Consensus Conference Nomenclature of Vasculitides. *Arthritis Rheum* 2013; 65: 1-11.
3. THICKETT DR, RICHTER AG, NATHANI N, PERKINS GD, HARPER L: Pulmonary manifestations of anti-neutrophil cytoplasmic antibody (ANCA)-positive vasculitis. *Rheumatology* (Oxford) 2006; 45: 261-8.
4. HOMMA S, SUZUKI A, SATO K: Pulmonary involvement in ANCA-associated vasculitis from the view of the pulmonologist. *Clin Exp Nephrol* 2013; 17: 667-71.
5. MOHAMMAD AJ, MORTENSEN KH, BABAR J *et al*.: Pulmonary involvement in antineutrophil cytoplasmic antibodies (ANCA)-associated vasculitis: the influence of ANCA subtype. *J Rheumatol* 2017; 44: 1458-67.
6. VAGLIO A, BUZIO C, ZWERINA J: Eosinophilic granulomatosis with polyangiitis (Churg-Strauss): state of the art. *Allergy* 2013; 68: 261-73.
7. FRANKEL SK, SCHWARZ MI: The pulmonary vasculitides. *Am J Respir Crit Care Med* 2012; 186: 216-24.
8. ALBA MA, FLORES-SUAREZ LF, HENDERSON AG *et al*.: Interstitial lung disease in ANCA vasculitis. *Autoimmun Rev* 2017; 16: 722-9.
9. MUSIAL J, WOJCIK K: Polish Vasculitis Registry: POLVAS. *Pol Arch Intern Med* 2017; 127: 71-2.
10. PADJAS A, SZNAJD J, SZCZEKLIK W, WOJCIK K, WAWRZYCKA K, MUSIAL J: Rare disease registries: an initiative to establish vasculitis registry in Poland. *Pol Arch Med Wewn* 2014; 124: 143-4.
11. WOJCIK K, WAWRZYCKA-ADAMCZYK K, WLUDARCZYK A *et al*.: Clinical characteristics of Polish patients with ANCA-associated vasculitides-retrospective analysis of POLVAS registry. *Clin Rheumatol* 2019; 38: 2553-63.
12. BIEDRON G, WLUDARCZYK A, WAWRZYCKA-ADAMCZYK K *et al*.: Treatment and its side effects in ANCA-associated vasculitides - Study based on POLVAS registry data. *Adv Med Sci* 2020; 65: 156-62.
13. REINHOLD-KELLER E, BEUGE N, LATZA U *et al*.: An interdisciplinary approach to the care of patients with Wegener's granulomatosis: long-term outcome in 155 patients. *Arthritis Rheum* 2000; 43: 1021-32.
14. LAI QY, MA TT, LI ZY, CHANG DY, ZHAO MH, CHEN M: Predictors for mortality in patients with antineutrophil cytoplasmic autoantibody-associated vasculitis: a study of 398 Chinese patients. *J Rheumatol* 2014; 41: 1849-55.
15. SACOTO G, BOUKHLAL S, SPECKS U, FLORES-SUAREZ LF, CORNEC D: Lung involvement in ANCA-associated vasculitis. *Presse Med* 2020; 49: 104039.
16. SCHIRMER JH, WRIGHT MN, VONTHEIN R *et al*.: Clinical presentation and long-term outcome of 144 patients with microscopic polyangiitis in a monocentric German cohort. *Rheumatology* (Oxford) 2016; 55: 71-9.
17. BLOCH DA, MICHEL BA, HUNDER GG *et al*.: The American College of Rheumatology 1990 criteria for the classification of vasculitis. Patients and methods. *Arthritis Rheum* 1990; 33: 1068-73.
18. GIOFFREDI A, MARITATI F, OLIVA E, BUZIO C: Eosinophilic granulomatosis with polyangiitis: An overview. *Front Immunol* 2014; 5: 1-8.
19. LANE SE, WATTS RA, SHEPSTONE L, SCOTT DG: Primary systemic vasculitis: clinical features and mortality. *QJM* 2005; 98: 97-111.
20. SOLANS-LAQUE R, FRAILE G, RODRIGUEZ-CARBALLEIRA M *et al*.: Clinical characteristics and outcome of Spanish patients with ANCA-associated vasculitides: Impact of the vasculitis type, ANCA specificity, and treatment on mortality and morbidity. *Medicine* (Baltimore) 2017; 96: e6083.
21. GUILLEVIN L, DURAND-GASSELIN B, CEVALLOS R *et al*.: Microscopic polyangiitis: clinical and laboratory findings in eighty-five patients. *Arthritis Rheum* 1999; 42: 421-30.
22. SHARMA A, NAIDU G, RATHI M *et al*.: Clinical features and long-term outcomes of 105 granulomatosis with polyangiitis patients: a single center experience from north India. *Int J Rheum Dis* 2018; 21: 278-84.
23. FURUTA S, CHAUDHRY AN, ARIMURA Y *et al*.: Comparison of the Phenotype and Outcome of Granulomatosis with Polyangiitis Between UK and Japanese Cohorts. *J Rheumatol* 2017; 44: 216-22.
24. FURUTA S, CHAUDHRY AN, HAMANO Y *et al*.: Comparison of phenotype and outcome in microscopic polyangiitis between Europe and Japan. *J Rheumatol* 2014; 41: 325-33.
25. HOFFMAN GS, KERR GS, LEAVITT RY *et al*.: Wegener granulomatosis: an analysis of 158 patients. *Ann Intern Med* 1992; 116: 488-98.
26. VILLIGER PM AND GUILLEVIN L: Microscopic polyangiitis: Clinical presentation. *Autoimmun Rev* 2010; 9: 812-9.
27. VAN DER GEEST KSM, BROUWER E, SANDERS JS *et al*.: Towards precision medicine in ANCA-associated vasculitis. *Rheumatology* (Oxford) 2018; 57: 1332-9.
28. GROH M, PAGNOUX C, BALDINI C *et al*.: Eosinophilic granulomatosis with polyangiitis (Churg-Strauss) (EGPA) Consensus Task Force recommendations for evaluation and management. *Eur J Intern Med* 2015; 26: 545-53.
29. WECHSLER ME, AKUTHOTA P, JAYNE D *et al*.: Mepolizumab or Placebo for Eosinophilic Granulomatosis with Polyangiitis. *N Engl J Med* 2017; 376: 1921-32.
30. KRONBICHLER A, KERSCHBAUM J, GRUNDLINGER G, LEIERER J, MAYER G, RUDNICKI M: Evaluation and validation of biomarkers in granulomatosis with polyangiitis and microscopic polyangiitis. *Nephrol*

Dial Transplant 2016; 31: 930-6.

31. LAUQUE D, CADRANEL J, LAZOR R *et al*.: Microscopic polyangiitis with alveolar hemorrhage. A study of 29 cases and review of the literature. Groupe d'Etudes et de Recherche sur les Maladies "Orphelines" Pulmonaires (GERM"O"P). *Medicine* (Baltimore) 2000; 79(4): 222-33.
32. FLORES-SUAREZ LF, RUIZ N, SALDARRIAGA RIVERA LM, PENSADO L: Reduced survival in microscopic polyangiitis patients with pulmonary fibrosis in a respiratory referral centre. *Clin Rheumatol* 2015; 34: 1653-4.
33. DEMISELLE J, AUCHABIE J, BELONCLE F *et al*.: Patients with ANCA-associated vasculitis admitted to the intensive care unit with acute vasculitis manifestations: a retrospective and comparative multicentric study. *Ann Intensive Care* 2017; 7: 39.
34. WLUDARCZYK A, POLOK K, GORKA J *et al*.: Patients with small-vessel vasculitides have the highest mortality among systemic autoimmune diseases patients treated in intensive care unit: A retrospective study with 5-year follow-up. *J Crit Care* 2018; 48: 166-71.
35. HOGAN SL, NACHMAN PH, WILKMAN AS, JENNETTE JC, FALK RJ: Prognostic markers in patients with antineutrophil cytoplasmic autoantibody-associated microscopic polyangiitis and glomerulonephritis. *J Am Soc Nephrol* 1996; 7: 23-32.
36. POLOK K, WLUDARCZYK A, SZCZEKLIK W: Clinical profile of patients with systemic autoimmune diseases treated in the intensive care unit who developed diffuse alveolar haemorrhage - an observational retrospective cohort study. *Anaesthesiol Intensive Ther* 2019; 51: 96-101.
37. FLOSSMANN O, BERDEN A, DE GROOT K *et al*.: Long-term patient survival in ANCA-associated vasculitis. *Ann Rheum Dis* 2011; 70: 488-94.