

## **Introduction**

ANCA-associated vasculitides (AAV) is a group of rare diseases of unknown etiology and autoimmune pathomechanism, which includes three entities - granulomatosis with polyangiitis (GPA), microscopic polyangiitis, (MPA) and eosinophilic granulomatosis with polyangiitis (EGPA).

AAV cause predominantly inflammation of the small vessels, which damage leads to the organ lesions, depending on the distribution of the inflammatory changes. Among the most common manifestations there are ENT, renal and pulmonary involvement, however, almost each organ may be involved in the course of this group of diseases. The significant advancement in the field of diagnostics and therapy of AAV have been made during the last several decades. These achievements, especially the possibility of administration of the immunosuppressive treatment have resulted in the improvement of the outcomes for patients with AAV, changing the status of these disorders from rapidly progressive and inevitably fatal to chronic, relapsing diseases. Despite this undeniable progress, the optimal treatment regimens are still being discussed and revised and long-lasting immunosuppressive treatment have become an important factor influencing mortality and morbidity. The aim of the study was the analysis of the treatment modalities and the associated side effects in a Polish nation-wide ANCA-associated vasculitides (AAV) patients' cohort. Moreover, the particular subgroups have been characterised – the patients with respiratory involvement and the group which needed stay at intensive care unit (ICU).

## **Materials and methods**

The data from retrospective branch of POLVAS registry have been used in this study. POLVAS is to date the largest ever created database, encompassing Polish population of AAV. Six hundred and twenty-five cases (417 with GPA, 106 with MPA and 102 with EGPA), with the diagnoses established between 1990 and 2016 years, were qualified for the assessment of the treatment and treatment-associated side effects. The data were obtained using retrospective questionnaires. The diagnoses of the particular entities were based on the American College of Rheumatology (ACR) criteria and 2012 Revised International Chapel Hill Consensus criteria. Three hundred and sixteen cases with radiological confirmation of AAV presence were selected for the analysis of the subgroup with respiratory involvement. Thirty cases from POLVAS database were included in the subgroup of AAV patients, who needed ICU stay and were analysed in the further part of the study. Standard descriptive statistics and statistic tools made for performing comparisons between groups were used. P-value <0.05 was assumed as

statistically significant (modified with Bonferroni correction when multiple comparisons were performed).

## Results

Treatment and treatment-associated side effects in the Polish population of AAV were characterised in the first part of the analyses.

The most frequently used medicaments in the remission induction treatment were glucocorticosteroids (GCS; 95.3%), cyclophosphamide (78.3%) and rituximab (9.3%). Patients with GPA and MPA were administered steroid pulses more frequently than those with EGPA (76.9% vs. 39.6%,  $p<0.01$  and 78.4% vs. 39.6%,  $p<0.01$ , respectively), as well as cyclophosphamide (85.7% vs. 43.1%;  $p<0.01$  and 83.0% vs. 43.1%  $p<0.01$ , respectively). On the other hand, methotrexate, azathioprine and GCS monotherapy were used more often in the EGPA group than GPA or MPA groups (for methotrexate: 15.7% vs. 5.3%,  $p<0.01$  and 15.7% vs. 0.9%,  $p<0.01$ , respectively; for azathioprine: 13.7% vs. 3.4%,  $p<0.01$  and 13.7% vs. 1.9%,  $p<0.01$ , respectively; for GCS monotherapy: 35.3% vs. 6.5%,  $p<0.01$  and 35.3% vs. 14.2%,  $p<0.01$ , respectively). Moreover, there was no case of rituximab nor plasmaphereses use during the remission induction phase in EGPA patients (compared to 12.8% cases of GPA and 4.7% cases of MPA with rituximab use as well as 13.8% cases of GPA and 15.1% cases of MPA with plasmaphereses use). Glucocorticosteroids, azathioprine and methotrexate were the most frequently administered drugs during maintenance therapy (the proportions in the whole group equalled to 84.3%, 37.8% and 23.0%, respectively). The proportion of cyclophosphamide use during the maintenance treatment was significantly lower in the cases with diagnosis established after 2010, compared to those with diagnosis made before 2004 or between 2004 and 2010 years (5.7% vs. 26.09%,  $p<0.01$  and 5.7% vs. 15.9%,  $p<0.01$ , respectively). The median cumulative dose of cyclophosphamide equalled 7.99g (4.18-14.0). Renal replacement therapy was required in 21.9% of all AAV cases. MPA patients predominated among patients requiring dialysis (MPA vs. GPA - 44.3% vs. 21.5%,  $p<0.01$ ). None of EGPA patients needed renal replacement therapy. The most common adverse effect of immunosuppressive treatment were infections – proportion of cases equalled 38.8% of the whole group. The infections' occurrence was associated with longer average observation time (OR=1.05, 95% CI 1.00-1.10,  $p=0.03$ ), GCS pulses administration (OR=2.83, 95% CI 1.73-4.64,  $p<0.01$ ) and renal replacement therapy (OR=1.725, 95% CI 1.10-2.71,  $p=0.02$ ).

The analysis, regarding Polish population of AAV with respiratory involvement was performed in the second part of the study. The prevalence of respiratory involvement (with radiological

confirmation) amounted to 68.5% of all AAV cases, 97.6% of EGPA cases, 67.8% of GPA cases and 40.0% of MPA cases. Constitutional symptoms, ENT, cardiovascular, gastrointestinal, central and peripheral nervous system involvement were reported more frequently in the group with respiratory involvement than in the group without such manifestation. The overall number of relapses was significantly higher in the group with respiratory involvement (medians: 1.0 [0.0-2.0] vs. 0.0 [0.0-1.0],  $p=0.01$ ). Moreover, statistically insignificant trends towards higher mortality (9.0% vs. 5.8%,  $p=0.25$ ), more frequent relapses requiring hospitalisation (48.7% vs. 41.8%,  $p=0.18$ ) and ICU stay (5.1% vs. 1.4%,  $p=0.12$ ) in this group were noticed. In the analysis of the combined group of GPA and MPA cases (EGPA cases excluded), the subgroup with respiratory involvement (compared to the subgroup without respiratory involvement) was characterised by higher median, maximal CRP concentration (46.0 mg/l [14.0-105.0] vs. 25.0 mg/l [6.6-75.1],  $p=0.01$ ), more frequent GCS use in remission induction (97.9% vs. 90.8%,  $p<0.01$ ), rarer GCS monotherapy (3.4% vs. 15.5%,  $p<0.01$ ), more frequent GCS pulses use (84.1% vs. 67.7%,  $p<0.01$ ), more frequent cyclophosphamide administration during remission induction phase (91.9% vs. 75.4%,  $p<0.01$ ) and more frequent IVIG use (8.1% vs. 2.1%,  $p=0.03$ ).

The description of cases with AAV who needed ICU stay was made in the third part of the study. More frequent respiratory, renal, central nervous system and eye involvement were observed in this group in comparison with the subgroup of cases who did not require ICU stay. In addition, more cases with infections (72.4% vs. 36.9%,  $p<0.01$ ) and higher mortality were present in the group which needed stay in ICU (53.6% vs. 7.8%,  $p<0.01$ ). IVIG treatment and hemodialysis were used more frequently in the group requiring ICU stay (17.2% vs. 4.8%,  $p<0.01$  and 48.3% vs. 21.8%,  $p<0.01$ , respectively).

## **Conclusions**

The treatment of Polish patients with AAV was predominantly in line with appropriate recommendations and reflected the changes in the guidelines. EGPA cases were treated less aggressively than GPA or MPA cases, which may suggest milder course of this entity in comparison with the other AAV. The most frequent side effect of the treatment were infections, which occurrence was associated with longer observation period, GCS pulses administration and renal replacement therapy. The prevalence of respiratory involvement (with radiological confirmation) amounted to 68.5% of all AAV cases and was highest in EGPA cases (97.6%), followed by GPA cases (67.8%) and MPA cases (40.0%). Patients' profile and more aggressive treatment in the combined GPA and MPA group suggest more severe course of disease in cases

with respiratory involvement compared to the subgroup without pulmonary manifestations. AAV cases treated in ICU (compared to those not requiring ICU stay) were characterised by more frequent involvement of crucial systems – respiratory, renal, CNS, more frequent infectious complications as well as higher mortality. Treatment regimens in this subgroup indicate the trend towards more intensive immunosuppressive therapy administration.