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Comorbidities in ANCA-associated vasculitis

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Abstract

The prognosis of patients with ANCA-associated vasculitis has improved over the past decades, but overall survival rates are still unsatisfactory. Recent research has focused on complications of immunosuppressive measures and comorbidities of ANCA-associated vasculitis. This review focuses on thromboembolic and cardiovascular events. A considerably increased risk of thromboembolic events has been reported, which is associated with active disease and impaired coagulation factors. There is mounting evidence that a hypercoagulable state is present even in patients in remission, and studies investigating the impact of tailored anticoagulation are needed to reduce the burden of thromboembolism. Cardiovascular mortality is one of the leading causes of death and accelerated atherosclerosis is frequently observed in patients with ANCA-associated vasculitis. A high frequency of patients develops hypertension, diabetes mellitus and hypercholesterolaemia, either as a consequence of immunosuppression or associated with the underlying disease. The current control of modifiable cardiovascular risk factors is insufficient and thorough reviews should be performed periodically. Treatment of these risk factors should be adopted according to current recommendations related to individual cardiovascular risk prediction.

Key words: comorbidity, hypertension, diabetes mellitus, vasculitis, coronary heart disease, deep vein thrombosis, pulmonary embolism, myocardial infarction, hypercholesterolaemia

Rheumatology key messages

- Cardiovascular events are among the leading causes of morbidity and mortality in ANCA-associated vasculitis.
- Active ANCA-associated vasculitis is linked with an increased risk of developing venous thromboembolic events.
- Cardiovascular risk factors in vasculitis need to be controlled to achieve the respective target values.

SUPPLEMENT

Introduction

Despite improved survival rates of patients with ANCA-associated vasculitis, comprising granulomatosis with polyangiitis (GPA), microscopic polyangiitis and eosinophilic granulomatosis with polyangiitis (EGPA), the overall mortality rate is still increased 2.7-fold in comparison with the general population [1]. Within the first year of diagnosis, infectious complications and active vasculitis are the leading causes of mortality, while thereafter cardiovascular events are the most common complication leading to death, followed by malignancies and infections. Severely impaired renal function, advancing age and high disease activity at baseline are independent predictors for patient survival [2]. A cohort of cases diagnosed from 2002 to 2017 confirmed that infections, malignancies and cardiovascular disease are the most common causes of death. A standardized mortality rate of 2.3 fold higher for cardiovascular mortality was reported, with a significant association of MPO-ANCA vasculitis with cardiovascular death, while a non-significantly increased mortality was reported for proteinase 3 (PR3)-ANCA positive disease. After adjustment for baseline creatinine, age and sex, cases with MPO-ANCA vasculitis retained a significantly higher risk of fatal cardiovascular events [3].

These findings highlight the importance of cardiovascular disease in the context of ANCA-associated vasculitis. In this review we will focus on early comorbidities associated with active disease, i.e. venous thromboembolic events (VTEs), and discuss the impact of inflammation on the onset of late comorbidities, strategies to diagnose cardiac involvement and the need to optimize management of cardiovascular risk factors to reduce the burden of cardiovascular events.

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Venous thromboembolic events

VTEs are frequently observed in patients with ANCA-associated vasculitis. The Wegenerã s Granulomatosis Etanercept Trial (WGET) trial enrolled patients with GPA and found an incidence rate of 8.9%, corresponding to 7.0 events per 100 person-years. The median time from enrolment during active disease to VTE was 2.1 months and there was a clear association of active disease and VTE [4]. In an analysis of the Danish National Hospital Register, Faurschou *et al.* observed incidence rate ratios of 25.7 and 20.2 for pulmonary embolism and deep venous thrombosis, respectively, within the first two years of diagnosis. Most vascular events occurred during episodes of treatment for active disease [5]. Further studies evaluated the association of VTEs and found an incidence rate of ∼8–10%. Several risk factors were identified, including patient's age, male sex, a history of VTE and stroke with motor deficit. A lower risk was described in those with lower limb motor neuropathy and a diagnosis of PR3-ANCA vasculitis [6]. A recent analysis of trials by the European Vasculitis Society (EUVAS) identified that CRP, higher baseline creatinine, and cutaneous and gastrointestinal involvement contributed to the risk of VTE. Among 417 participants with complete datasets, 41 (9.8%) VTEs occurred [7]. Recent studies aimed to understand the hypercoagulable state of patients with ANCA-associated vasculitis and identified several mechanisms. A number of patients with ANCA-associated vasculitis have presence of anti-plasminogen and anti-tissue plasminogen activator antibodies, and exhibit retarded fibrinolysis. Anti-plasminogen antibody positivity was more frequent in patients with severely impaired renal function at baseline [8]. The alternative complement pathway is crucially involved in disease pathogenesis. Mechanistic studies revealed that C5a-primed neutrophils produce tissue factor-expressing microparticles and neutrophil extracellular traps, both crucially involved in perpetuating inflammation, after stimulation with ANCA. Tissue factor-expressing microparticles and neutrophil extracellular traps were capable of inducing thrombin generation [9]. During active disease, crucial coagulation parameters are impaired, including increased platelet counts, fibrinogen, prothrombin fragments and D-dimer. Higher levels of factor VIII, von Willebrand factor, and ristocetin cofactor activity and antigen persist during vasculitis remission [10]. Analysis of coagulation factors during stable remission revealed increased levels of endogenous thrombin potential, factor VIII and tissue factor pathway inhibitor in patients with ANCA-associated vasculitis [11]. This not only underlines the impact of active disease on the coagulation status, but also reveals that patients in stable remission are hypercoagulable and may exhibit a higher VTE risk.

Myocardial infarction and stroke

Elderly patients with ANCA-associated vasculitis are at an increased risk of developing cardiovascular disease [12]. Using health care data from British Columbia, Aviña-Zubieta *et al.* [13] reported an increased incidence of myocardial infarction in a fully adjusted model (even for outpatient visits and glucocorticoid use) of patients with GPA with a relative risk (RR) of 1.86, while the rate of ischaemic stroke was non-significantly increased (RR of 1.50). Most events occurred within the first year of diagnosis, with a steady decrease in the incidence during the following years. The risk for ischaemic heart disease in GPA was further studied by using the Danish National Hospital Register. Overall, a 1.9-fold increased risk was reported, and this was mainly attributable to acute myocardial infarction and other diagnoses listed within International Classification of Diseases 8/10 blocks of ischaemic heart disease. Among risk factors, elderly patients $\geq$50 years at the time of diagnosis, male sex and patients receiving a high cumulative dose of CYC ($>$36 g) were identified as significant predictors [14]. Again, the incidence of stroke either in the first two years after diagnosis or thereafter did not differ from a matched background population, with an incident rate ratio of 1.4 [5].

In contrast, the calculated comparative morbidity figure (CMF) in a cohort study from southern France revealed increased rates of ischaemic stroke incidence (CMF 4.65) and, in line with reports from other databases, coronary artery disease (CMF 4.22). Smoking at the time of diagnosis was an independent predictor of major cardiovascular event and as expected, a history of coronary artery disease was associated with another event during follow-up [15]. In a retrospective analysis with a matched cohort comprising patients with chronic kidney disease, an excess of cardiovascular events with a hazard ratio of 2.23 for the cohort with ANCA-associated vasculitis could be confirmed. A history of cardiovascular disease, dialysis dependency and smoking were associated with cardiovascular events. Elderly patients, those with a lower estimated glomerular filtration rate and higher serum cholesterol levels at baseline were particularly at an increased risk [16].

A recent meta-analysis of observational studies highlighted an increased risk for all cardiovascular events. The RR of ischaemic heart disease was elevated (RR of 1.60), while there was a trend towards more cerebrovascular accidents (RR of 1.20) [17]. While an increase in cardiac events was observed in all studies, the impact of vasculitis on the risk of cerebrovascular disease needs to be investigated in larger studies with well-defined populations. Again, several mechanistic studies have emerged in the past suggesting explanations for the increased risk of cardiovascular disease in patients with ANCA-associated vasculitis. Carotid intima-media thickness measurements in GPA patients during remission revealed increased intima-media thickness compared with matched controls, and these alterations were

associated with raised levels of biomarkers indicating inflammation [18]. Endothelium-dependent vasodilatation was impaired in patients with GPA and EGPA as measured at two different sites, and inversely correlated with age [19]. In active disease, the augmentation index and the pulse wave velocity were elevated, while the aortic timing of the reflected waveform was decreased. These changes normalized upon remission and did not differ from analysis of matched controls [20].

Why should we perform cardiac imaging?

Echocardiography is a helpful tool to detect structural cardiac abnormalities. A cross-sectional study found lower left-ventricle ejection fraction, higher right ventricle systolic pressure, higher mean E/E′ ratio as a sign of higher left ventricle filling pressure, and increased frequencies of valvular regurgitation in patients with ANCA-associated vasculitis compared with age- and gender-matched controls assessed within a period of 3 months from initial diagnosis. Pericardial effusion and left ventricular hypertrophy were present in one-fifth of the subjects. Differences among disease phenotypes were reported [21]. A prospective cohort study including 50 EGPA and 41 GPA patients in remission used a step-up approach to investigate cardiac involvement. ECG and echocardiography identified cardiac involvement in 62% EGPA and 46% GPA patients, which was further increased to 66 and 61% in cases undergoing cardiac MRI. Upon indication, endomyocardial biopsies and coronary artery assessment were performed and found a significant proportion of abnormalities. Cardiac involvement assessed by ECG or echocardiography in patients with ANCA-associated vasculitis was a strong predictor for all-cause and cardiovascular mortality during follow-up [22]. Cardiac MRI revealed reduced left-ventricle ejection fraction values in subjects with late gadolinium enhancement. While late gadolinium enhancement was present in 43% of patients in a cross-sectional study, a large proportion of cases with EGPA and GPA presented higher native T1 and T2 mapping values, which are suggestive for both chronic (fibrosis) and acute (inflammation) changes in the myocardium [23].

Are we adequately controlling cardiovascular risk factors?

A recent study investigated the change in the lipid profile of participants from the Rituximab for ANCA-Associated Vasculitis (RAVE) trial. A significant increase of total cholesterol, low-density lipoprotein and apolipoprotein B was observed from baseline to month 6. Further analysis highlighted that these changes in the above-mentioned parameters are only observed in patients with a new diagnosis of ANCA-associated vasculitis (+19, +32 and +12%, respectively). PR3-ANCA-positive vasculitis and patients achieving remission off steroids by month 6 had increases in total cholesterol, low-density lipoprotein and apolipoprotein B, while this was not observed in cases with MPO-ANCA vasculitis or those not achieving remission without steroids [24]. This underlines the importance of regularly controlling lipid parameters once patients achieve remission. Factors such as fasting or weight loss during active disease impair cholesterol synthesis, which may explain lower levels at baseline. Assessing the cardiovascular risk of patients with ANCA-associated vasculitis seems pivotal to reduce the increased risk of cardiovascular events and mortality. Long-term follow-up of six EUVAS trials identified 302 patients followed for a mean of 7.1 years. The frequency of hypertension and diabetes increased by 36.7 and 9.3%, respectively, over time [25]. A recent multicentre study aimed to investigate the management of cardiovascular risk factors in patients with ANCA-associated vasculitis compared with a control group comprising patients with hypertension. Almost one-third of participants with ANCA-associated vasculitis were at very high 10-year cardiovascular risk and more patients had hyperlipidaemia compared with the control group. A majority (75.7%) had a low-density lipoprotein-cholesterol target according to their cardiovascular risk level, but only 10% of these patients achieved their target levels. Lipoprotein(a) levels were elevated in a quarter of patients with ANCA-associated vasculitis. A better control of hypertension was recorded in cases with an albumin excretion rate <30 mg/day. Over 75% reached the target blood pressure of $\leq$140/90 mmHg, while among those with an albumin excretion rate of >30 mg/day only 7/20 patients achieved their proposed target blood pressure of $\leq$130/80 mmHg [26]. This study clearly highlights that systematic assessment of a patient's individual cardiovascular risk needs to be performed periodically, and medication needs to be adopted accordingly. In order to assess the potential efficacy of lipid-lowering measures, the French Vasculitis Study Group is currently conducting a randomized controlled trial (STATVAS, NCT02117453), which is assigning patients in remission to either rosuvastatin 20 mg/day or placebo. The primary endpoint is defined as change in mean intima-media thickness for six predefined sites after 24 months. Several secondary outcome measures will assess potential differences in both groups.

Conclusion

In recent years, research in ANCA-associated vasculitis has focused on comorbidities attributable to these diseases. Early and late onset comorbidities have a significant impact on quality of life, morbidity and mortality rates. The latter is still unsatisfactory, and cardiovascular complications are among the principal complications leading to death [1, 2]. VTEs generally occur during disease activity [4] and there is a strong need to identify potential predictors that would allow for risk stratification. Studies focusing on this complication are on the way and further mechanistic work is necessary to

potentially provide tailored anticoagulation weighting risk (i.e. increased bleeding risk) and benefit. Mortality due to cardiac events is still increased, and accelerated atherosclerosis and impaired vasodilatation [18, 20] are proposed mechanisms leading to cardiovascular disease. The frequency of cardiovascular involvement has been underestimated and further diagnostic approaches should be considered in patients at risk [22]. Recent studies highlighted that patients with ANCA-associated vasculitis frequently develop cardiovascular risk factors as a consequence of immunosuppressive treatment and that these risk factors are poorly controlled. We suggest that cardiovascular risk factors are determined in detail periodically (i.e. every 6 months), and that medication to treat hypercholesterolaemia, hypertension and diabetes mellitus is adjusted to achieve respective target values. Moreover, the importance of general and lifestyle modifying measures needs to be accentuated, and patients should be advised to stop smoking and perform regular exercise.

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