Coronary Artery Disease in Granulomatosis with Polyangiitis: a Review

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Accepted: 7 March 2022 / Published online: 16 March 2022 © The Author(s) 2022

Abstract
Granulomatosis with polyangiitis is an immunologically mediated small to medium vessel vasculitis associated with the formation of antineutrophil cytoplasmic antibodies. Advances in immunosuppressive therapy have expanded patients’ life expectancy in recent decades and have required an expansion of clinical attention to include management of chronic disease manifestations and long-term comorbidities. Though the heart and coronary arteries specifically are typically not primarily affected in GPA, studies have shown that patients are at an increased risk of cardiovascular and thromboembolic events. In many patients, metabolic risk factors promoting the formation of atherosclerotic plaques are not sufficiently controlled or screened for and potentially exacerbated by undesired treatment effects. This review aims to provide clinical physicians with an overview of the current literature on epidemiology, pathophysiology and prevention of coronary artery disease in the context of granulomatosis with polyangiitis and help to identify and lower the risk of cardiovascular events in this high-risk population.

Keywords Coronary artery disease · Granulomatosis with polyangiitis · Atherosclerosis · Myocardial ischemia · Anti-neutrophil cytoplasmic antibody-associated vasculitis

Introduction
Granulomatosis with polyangiitis (GPA) is a necrotising vasculitis of small to medium-sized blood vessels. GPA is highly associated with antineutrophil cytoplasmic antibodies (ANCA) and constitutes a clinical phenotype of ANCA-associated vasculitis (AAV) alongside microscopic polyangiitis and eosinophilic granulomatosis with polyangiitis [1].

GPA used to be lethal in a matter of months back in the early twentieth century when Friedrich Wegener, a German pathologist, first described the condition in detail which became known as “Wegener’s Granulomatosis” [2, 3]. Through the introduction of effective immunosuppressive agents and widespread availability of renal replacement therapy, GPA has become a chronic condition characterised by periods of remission and relapse [4].

While GPA is still generally considered a rare disease, epidemiologic studies show an increase in prevalence over the last decades [5]. Australia, New Zealand, and northern Europe are among the most affected regions worldwide with prevalence reaching close to 100 per million [6, 7]. Patients diagnosed with GPA are at an approximately fourfold increased risk of suffering cardiovascular events compared to the general population [8].

Clinical Presentation and Cardiac Manifestations
Typical disease manifestations include necrotising granulomatous lesions of the upper or lower respiratory tract and glomerulonephritis. Patients may present with nasal or oral ulcers, purulent or bloody nasal discharge, cough, pulmonary haemorrhage, musculoskeletal pain or abnormal renal function. Generic symptoms may comprise malaise, anorexia and fever of unknown origin [9, 10]. Patients develop persistent disease manifestations including proteinuria and impaired glomerular filtration, nasal crusting, hypertension, hearing loss or peripheral polyneuropathy. Some long-term complications are attributed to undesired treatment effects,
especially osteoporosis, hypertension, diabetes, infections and malignancy [11]. At onset of symptoms, the patients’ median age is 40–50 years [10], highlighting the significance of prolonged disease management.

Though involvement of the upper respiratory tract is most common, GPA can affect almost any organ including the cardiovascular system [4]. The most common cardiac manifestations are pericarditis and myocarditis followed by coronary artery disease (CAD), local or global wall motion abnormalities, conduction abnormalities and valvular heart disease [12]. Some authors report rare cases of patients developing coronary artery aneurysms, coronary artery dissection and endocarditis [13–15]. Clinical cardiovascular manifestations affect about 3% of patients [5, 12]. However, according to one study, depending on modalities used, up to 46% of GPA patients in remission have detectable cardiac involvement if examined using ECG and echocardiography. Cardiac abnormalities include the following:

- **Major ECG abnormalities**
- **Pericardial effusion**
- **(peri-)Myocarditis**
- **LGE and/or oedema**
- **Regional or global wall motion abnormalities**
- **Significant valvar regurgitation**
- **Pulmonary hypertension**
- **Significant coronary lesion(s) (CT-angiography and/or coronary angiogram on indication)**
- **Moderate to severe diastolic dysfunction (grade ≥ 2)**

In control patients matched for age-, sex-, and cardiovascular risk, only 20% showed cardiac abnormalities. In the absence of symptoms, about 40% of patients still had detectable cardiac involvement using ECG and echocardiography. Of patients presenting without symptoms and major ECG findings, about half of the examined GPA-patients had signs of cardiac involvement in in-depth screening using cardiac magnetic resonance imaging (CMR) [16]. Another CMR study of patients diagnosed with GPA and a matched control population found increased extracellular volume fraction (ECV), an indication of oedema and early diffuse myocardial fibrosis, in 24% of patients compared to none in the group of healthy volunteers. Late gadolinium enhancement (LGE), a marker for focal fibrosis, was detectable in 32% of patients. In none of them, findings were suggestive of ischaemic myocardial damage [17].

### Mortality, Morbidity and Relapse

In patients diagnosed with AVV, both vasculitis and therapy-associated adverse events account for increased mortality. Mortality is highest following initial diagnosis driven by infection and progressive organ damage with a reduction of relative risk after 1 year [18]. Long-term excess mortality is determined by infection, malignancy and cardiovascular disease [19].

Though there was considerable improvement in survival over time between 1997 (HR 5.61 [95% CI: 3.14–10.04]) and 2012 (HR 2.33 [95% CI: 1.53–3.55]), overall mortality remains increased compared to the general population [20]. In their cohort study of patients diagnosed with either microscopic polyangiitis or GPA, Mourguet et al. (2019) have shown that compared to the general population, both CAD and ischaemic stroke equally occur about four times more frequently in both groups. Cumulative incidence of major cardiovascular events defined as acute CAD, ischemic stroke or peripheral vascular disease requiring revascularisation was at 7%, 15% and 23% of patients after 1, 5 and 10 years, respectively [8]. A meta-analysis of over 14,000 patients with AVV reports a relative risk of 1.65 (95% CI: 1.23–2.22) for all cardiovascular events compared to the general population [21]. Another GPA-specific cohort study found significantly elevated risk for myocardial infarction (HR: 1.86 [95% CI: 1.05–3.31]) highest within 1 year after diagnosis. Risk for stroke however remained insignificantly elevated [22].

Higher Birmingham Vasculitis Activity Score, dyslipidaemia, body-mass index (BMI) and family history of cardiovascular disease proved to be predictive factors of cardiovascular disease [23, 24]. Disease manifestations affecting the ear, nose or throat showed to be protective in one study but not in others [8]. Compared to myeloperoxidase-specific ANCA (MPO-ANCA) positive and ANCA negative patients, patients with positive proteinase 3-specific ANCA (PR3-ANCA) might be at lower cardiovascular risk overall [25]. However, both of these findings were inconsistent among different studies and require further investigation [23].

In a recent analysis of hospitalisations due to GPA, about one in five patients were concurrently diagnosed with CAD. Compared to all patients diagnosed with CAD, those previously diagnosed with GPA had fewer or less marked generic cardiovascular risk factors like hypertension, hyperlipidaemia, diabetes mellitus and history of smoking but were more likely to suffer from chronic kidney disease. Within a 10-year period, among all hospitalisations of patients with GPA, the proportion of those concurrently diagnosed with CAD increased by about 36% while remaining unchanged in the general population [26].

Pierrot-Deseilligny Despujol et al. (2010) have shown that acute cardiac non-vascular disease manifestations (peri-carditis, myocarditis and heart failure) are an independent risk factor for relapse (HR: 2.9 [95% CI: 1.3–6.5]) after achieving remission [27]. However, these findings could not be confirmed in other studies [12] and it yet remains unclear.
whether these manifestations of GPA also increase risk for cardiovascular events specifically.

Pathophysiology

ANCA have shown to be not only diagnostic for AVV, but pathogenic in mouse models [28]. However, ANCA of lower titre and avidity might be detected in healthy individuals as well [29, 30], and more than one in ten GPA patients have no detectable ANCA [5]. While ANCA have high diagnostic value, serial measurements for prognostic reasons are still disputed [31]. While the initial mechanisms causing ANCA sensitisation are not yet well understood, recent studies have shown an association between pre-existing autoimmune conditions, renal function impairment and sinus infections [32]. There are some hints that the composition of nasal microbiota and especially staphylococci may influence the course of remission and relapse [33, 34].

Vasculitis is triggered by ANCA binding to neutrophils which in turn degranulate and produce reactive oxygen species (ROS). This leads to endothelium activation, neutrophil adhesion and transmigration, ultimately resulting in vascular inflammation [35]. In this process, neutrophils release pro-inflammatory cytokines and neutrophil extracellular traps (NET) which in turn induce inflammation, activation of dendritic cells and monocytes, endothelial damage and complement activation [36, 37].

Endothelial Dysfunction and Inflammation

Inflammation is considered a key driver of atherosclerosis and is exacerbated in vasculitis [38]. Pro-inflammatory cytokines, NETs and complement activation cause endothelial damage and upregulation of selectins, vascular cell adhesion molecule-1 (VCAM-1) and thrombomodulin. This promotes leukocyte attachment and transmigration resulting in further inflammation, vascular remodelling and ultimately formation of atherosclerotic plaques [39].

Endothelium plays a crucial role in regulation of blood flow, vascular tone and thrombosis [40]. Due to the inflammatory process, however, endothelial function is impaired [38]. In patients with GPA, soluble markers of endothelial injury are significantly elevated [41]. Levels strongly correlate with elevation of C-reactive protein (CRP) and interleukin 6 (IL-6) which are independently associated with plaque formation [42]. Endothelial dysfunction is characterised by increased permeability due to leukocyte invasion, opening of intercellular junctions and retraction of cellular extensions [43]. This promotes subendothelial accumulation of atherogenic lipids and is considered a hallmark of atherogenesis [38].

Vascular Tone and Haemostasis

Endothelium also plays a crucial role in local regulation of vascular tone. Under shear stress, the glycocalyx induces nitric oxide (NO) and prostacyclin (PGI2) synthesis. Both NO and PGI2 inhibit platelet aggregation and NO dilates the vessel, reduces smooth muscle cell proliferation and counteracts inflammation [44, 45]. NO is considered vasoprotective under physiological conditions but may induce disruption of the endothelial surface layer when production is sustained [46, 47].

The luminal endothelial surface is covered with negatively charged glycoproteins and proteoglycans, referred to as the glycocalyx. It plays a crucial role in blood-endothelium interaction by binding serum proteins including antithrombin 3, fibroblast growth factor and superoxide-dismutase thus inhibiting coagulation, inflammation and leukocyte adhesion [48]. Inflammatory processes cause glycocalyx degradation and render the endothelium more vulnerable to lipid accumulation through increased permeability [49–52].

Measurement of brachial artery flow-mediated dilatation (FMD) is an established tool for the assessment of endothelial function and predictor of cardiovascular events [53]. Pacholczak et al. (2018) have shown that FMD is significantly lower in GPA patients compared to a matched control group and is inversely correlated with disease duration, serum levels of CRP, IL-6, VCAM-1 and creatinine as well as pack-years of smoking and diabetes [41].

In their investigation of deep venous thrombosis in AVV, Hilhorst et al. (2013) have shown that patients in remission have higher thrombin generation potential compared to a healthy control group [54]. Higher thrombin generation in vitro is indicative of a pro-coagulatory state in vivo [55]. In addition, von Willebrand factor and factor 8 are also elevated in patients with AVV, findings suggestive of endothelial activation, dysfunction or damage [56, 57]. During active disease, levels of prothrombin fragments and D-dimer are elevated and correlate negatively with estimated glomerular filtration rate (eGFR). These findings point towards increased thrombin formation and fibrinogen turnover during active disease [58].

About 25% of AVV patients develop antibodies targeted at plasminogen and—to a lesser extent—tissue plasminogen activator during relapse. Both antigens play a vital role in fibrinolysis and inhibition of the respective pathways showed to slow clot lysis in vitro. In biopsies, a higher percentage of glomeruli showed fibrinoid necrosis compared to patients who tested anti-plasminogen sero-negative [59]. Plasminogen protects the glomerulus from inflammatory injury and clears fibrin exudate reducing glomerular fibrosis and necrosis [60, 61]. Overall, anti-plasminogen
positivity was not only associated with more severe renal dysfunction but also more active systemic disease [62].

**Microparticles in Systemic Vasculitis**

There is growing evidence that microparticles (MPs) might play an important role in systemic vasculitis and link autoimmunity, inflammation and hypercoagulability [63]. Upon cell activation, apoptosis or exposure to shear stress, endothelial cells, leucocytes, platelets and even erythrocytes release small plasma membrane vesicles. They present surface glycoproteins and receptors distinctive of their parent cell and contain plasmatic components like enzymes, transcription factors or mRNA. MPs are considered to contribute to cell–cell interaction influencing coagulation, inflammation and autoimmunity [64, 65].

In GPA patients in relapse, MP counts are elevated compared to patients in remission and correlate with disease activity and markers of inflammation. Through the expression of adhesion molecules, tissue factor and cytokines, MPs regulate inflammation and coagulation and influence both endothelial and leucocyte behaviour. Levels of platelet-derived MPs (PMPs) and, to a lesser extent, leucocyte-derived MPs (LMPs) and endothelial cell-derived MPs (EMPs) correlate with disease activity and markers of inflammation [66]. PMPs are closely linked to platelet reactivity and release of cytokines resulting in a pro-thrombotic state and promote atherosclerosis through increased lipid accumulation and formation of foam cells [67, 68]. Release of LMPs has been shown to increase expression of ANCA-antigens on neutrophils in vitro and might therefore boost neutrophil activation [69]. EMPs are promoting neutrophil chemotaxis, propelling inflammatory processes [70].

**Renal Impairment and Systemic Inflammation**

Crescentic necrotising pauci-immune glomerulonephritis is considered a hallmark in GPA [9]. Renal involvement is characterised by impaired kidney function, proteinuria and blood or red cell casts in urinalysis and may clinically present as acute kidney injury, chronic kidney disease or end-stage renal failure. Over 60% of GPA patients suffer from chronic kidney disease [4, 10] and about a quarter progress into end-stage renal failure. Kidney transplantation is often required and is associated with a reduction in overall mortality of 70% [71]. Severe renal involvement is associated with a higher risk of relapse once remission is achieved [72]. Impaired kidney function has also been shown to be an independent risk factor for cardiovascular events, both in the general population and in GPA specifically [25, 73].

**Complement System**

The complement system used to be considered to play a minor role in pathogenesis due to minimal immune deposits in renal biopsy. However, experiments in murine disease models have shown that both mice with induced deficiency of complement factor three and complement factor five knock-out mice were not susceptible to induction of necrotising crescentic glomerulonephritis via transfer of anti-MPO antibodies [74]. Ohlsson et al. (2019) have shown that ANCA-stimulated neutrophils from AVV patients have the ability to activate the alternative pathway. This effect proved to be proportionate to the release of LMPs [75]. Increased activation of complement factors and therefore activation of anaphylatoxins capable of activating more neutrophils is suggested to create a vicious circle of inflammation [76]. These findings have led to the development of new therapeutic agents intercepting the alternative pathway inhibiting the C5a receptor 1 which are described below [77]. Furthermore, hypocomplementaemia, though relatively rare even among AVV patients, was associated with significantly more severe renal disease manifestations and worse overall survival [78].

**Treatment and Reduction of Cardiovascular Risk**

GPA presentation is widely variable among patients with symptoms ranging from subclinical to acutely life-threatening. This ought to be represented in individual treatment regimens which usually involve potent immunosuppressive drugs. Even in patients in remission, quality of life may be severely impaired, either due to disease manifestations or side-effects of treatment [79].

**Brief Overview of Guidelines**

Scientific societies from Europe, Great Britain, Canada and Brazil have published guidelines and recommendations covering all aspects of clinical diagnosis and treatment. Though guidelines agree on the key points, there is some dissent on aspects of glucocorticoid tapering regimens, intervals of routine assessment during different stages of disease and treatment of children and the pregnant as these groups are largely excluded in clinical trials [80].

Induction therapy is the immediate treatment for new-onset disease or acute relapse. For organ- or life-threatening disease, the recommended treatment is high-dose glucocorticoids in combination with either cyclophosphamide or rituximab. In non-organ-threatening disease, a combination of glucocorticoids and either methotrexate or mycophenolate mofetil is recommended [81]. Once patients are in remission,
maintenance therapy aims to prevent relapse. Current European guidelines recommend a low-dose glucocorticoid regimen combined with either azathioprine, rituximab, methotrexate or mycophenolate mofetil for at least 2 years after induction of remission [81]. Evidence on the ideal duration of maintenance therapy is lacking; however, there is solid evidence that prolonged therapy is effective in reduction of relapse risk [82–85].

Therapeutic regimens as well as individual risk profiles are highly variable among patients. Due to the disease’s relative rarity and high complexity, management of patients at or in collaboration with centres of expertise is recommended. For many patients, participation in clinical trials may be sensible [81].

**Glucocorticoid-Associated Toxicity**

Glucocorticoids are a pillar of therapy in GPA as they act rapidly and are broadly available. However, treatment regimens featuring glucocorticoids for extended periods of time are associated with undesirable side effects including psychiatric disorders, osteoporosis and metabolic disturbance leading to diabetes, dyslipidaemia and hypertension [86]. This prompts the assumption that prolonged glucocorticoid therapy may contribute towards atherogenesis and overshadow advantageous anti-inflammatory properties to some extent [87–89]. Prolonged maintenance therapy and is also associated with significantly increased risk of infections including urinary tract infections, pneumonia and sepsis [90, 91].

**Cyclophosphamide-Associated Toxicity**

Cyclophosphamide is recommended in induction therapy in organ- or life-threatening disease alongside high-dose glucocorticoids [81]. Cyclophosphamide is used as an antitumor drug and in other autoimmune diseases including rheumatoid arthritis and multiple sclerosis. Cumulative dosage is limited by cardiotoxicity which may lead to heart failure and death. The agent has also been found to cause endothelial and mitochondrial dysfunction. Endothelial permeability increases due to oxidative stress and leucocyte adhesion is promoted. Release of vasoactive substances including NO and endothelin-1 is altered and may ultimately exacerbate pre-existing endothelial dysfunction and ultimately promote atherogenesis [92].

**Cardiovascular Comorbidities**

Overall disease activity measured as Birmingham Vasculitis Activity Score is an important predictor of cardiovascular events [93]. A higher score is an indicator of systemic organ involvement and reflective of higher levels of inflammation also causing accelerated atherosclerosis [38]. Therefore, effective immunosuppressive therapeutic regimens preventing relapse and lowering disease activity are likely to be effective in reducing cardiovascular risk.

Conventional cardiovascular risk factors are exacerbated in GPA [11]. Patients are at increased risk for hypertension (HR 2.45 [95% CI: 1.84–3.26]), type 2 diabetes (HR 2.13 [95% CI: 1.36–3.32]) and dyslipidaemia (HR 1.98 [95% CI: 1.29–3.04]) [94]. Most guidelines recommend that patients ought to be assessed for cardiovascular risk factors on a regular basis [80, 81]. However, management is often insufficient, as Bramlage et al. (2017) have shown. Even patients at high or very high risk for cardiovascular events rarely meet their respective low-density lipoprotein cholesterol or blood pressure goals as defined in Kidney Disease: Improving Global Outcomes guidelines. Control of metabolic risk factors may be challenging and require close clinical attention due to drug interactions or impaired renal function compromising pharmacokinetics [95–97].

**Recent Advances in Therapy**

Though glucocorticoids are used extensively in different immunosuppressive regimens and stages of GPA, guidelines acknowledge that evidence on dosage, oral versus intravenous administration and duration is scarce [80, 81]. More rapid tapering regimens after episodes of severe AVV have shown to be non-inferior to standard treatment while markedly reducing overall glucocorticoid dosage and associated toxicity [98, 99]. In addition to standard remission induction therapy in severe AVV, additional intravenous pulses of high-dose methylprednisolone showed to be associated with greater risk of infection and did not improve outcome [100].

In maintenance therapy, prolonged administration of low-dose glucocorticoids is currently disputed [91]. The ongoing prospective randomised “The Assessment of Prednisone in Remission Trial” (TAPIR, NCT01933724) will evaluate the clinical value of glucocorticoids in preventing relapse and weigh advantages against associated toxicity.

Cyclophosphamide has been considered the gold standard of induction therapy for decades but is also associated with major toxicity as described previously. Stone et al. (2010) have shown that rituximab plus glucocorticoids has similar efficacy compared to cyclophosphamide plus glucocorticoids in induction of remission [101]. Depending on availability, rituximab may therefore be the treatment of choice in induction therapy compared to cyclophosphamide [102].

New insights into the complement system’s involvement in pathogenesis in animal models as described previously have led to the discovery of new therapeutic targets [103]. The small molecule and inhibitor of C5a receptor 1 avacopan added to a standard induction scheme of cyclophosphamide or rituximab without glucocorticoids was non-inferior compared to standard induction therapy plus glucocorticoids in a
preliminary study. Avacopan was well tolerated and patients reported more pronounced improvement in health-related quality of life compared to the standard treatment control group [77]. A randomised phase 3 trial is currently under way and will evaluate if avacopan could replace glucocorticoids in maintenance therapy [104].

Quality of Life and Psychosocial Factors

AVV patients often experience a severe reduction in health-related quality of life (HRQoL) suffering from sleep and mood disorders, fatigue and disease-associated unemployment [105]. Fatigue seems to be related to a central cause rather than abnormal muscle or cardiorespiratory function [106]. Encouraging physical activity may offer some improvement, however, yet only preliminary studies exist [107]. HRQoL is also determined by disease status and activity but the severity of HRQoL reduction is at least partly determined by the availability of support of physicians and relatives [108].

Psychological support and physical activity as an integral component of comprehensive patient management could be advantageous in improving overall quality of life. To date, there is very limited evidence on these interventions’ effects but it may be hypothesised that physical activity could help counter the prevalence of cardiovascular risk factors and therefore improve overall mortality.

Conclusion

More profound knowledge of pathogenesis in GPA and rapid evolvement of therapeutic strategies have enabled physicians to transform what used to be a deadly disease into a chronic condition some patients may live with for decades. Chronic disease manifestations however still severely affect many patients, and therapy-associated adverse events account for a significant proportion of overall mortality. Cardiovascular disease is among the most frequent causes of death in GPA patients with risk factors often not sufficiently treated. Revisited therapeutic regimens and the emergence of new targeted immunomodulatory agents may be able to curb therapy-associated damage in the long-run while also lowering risk of relapse. Until then, GPA patients need to be screened consistently for individuals with exceeding cardiovascular risk and close attention needs to be paid to the reduction of metabolic risk factors for cardiovascular disease in this high-risk population.

Author Contribution All work was done by Michael H. Poledniczek, including but not limited to the initial idea, conceptualisation, literature research and analysis and drafting and revision of the manuscript.

Funding Open access funding provided by Medical University of Vienna.

Data Availability Not applicable.

Code Availability Not applicable.

Declarations

Ethics Approval Not applicable.

Consent to Participate Not applicable.

Consent for Publication Not applicable.

Conflict of Interest ICJME Conflict of Interest form attached.

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