The AAV comprise a heterogeneous group of the three distinct forms, namely microscopic polyangiitis (MPA), granulomatosis with polyangiitis (GPA, formerly: Wegener’s granulomatosis) and eosinophilic granulomatosis with polyangiitis (EGPA, formerly Churg-Strauss syndrome) [1,2]. From the clinical point of view and according to the disease definitions and classification criteria, they share the manifestation of small- to medium-size vessel vasculitis which is strongly associated with anti-neutrophil cytoplasm antibodies (ANCA). Whereas MPA has no additional features and seems to represent a mere vasculitic disease, GPA is characterised by a granulomatous inflammatory process predominantly occurring in the upper and lower respiratory tract and asthma, eosinophilia and granulomatous inflammation are additional hallmarks of EGPA [1,2]. Interestingly, GPA and EGPA seem to follow a stage-wise course [3–6]: In GPA, the initial stage is referred to as localized GPA which is defined by upper and lower respiratory disease and no clinical signs of vasculitis [3]. Nearly half of the patients with localized disease are ANCA-negative [7]. Upon the evolvement of vasculitic symptoms (early systemic, generalized and severe disease), the vast majority of patients are ANCA-positive. Persistent localized disease in GPA is rare (5% of patients) [7]. Therefore, GPA cohorts are mainly represented by patients with systemic, ANCA-positive disease. Asthma followed by marked eosinophilia and subsequent vasculitis manifestations marks the disease course in EGPA. A predominant vasculitic phenotype with strong ANCA association can be distinguished from a phenotype with predominant eosinophil-associated organ manifestations that is usually ANCA-negative. All in all, only 40% of EGPA patients are ANCA-positive [8,9].

In MPA, which is characterised by systemic vasculitis manifestations only, most patients are ANCA-positive [10]. Therefore, seronegative AAV is mainly represented by the initial stages of GPA and EGPA and the “eosinophilic” EGPA phenotype.

It is not clear why GPA has a strong association with ANCA directed against proteinase 3 (PR3-ANCA) whereas MPA and EGPA are predominantly associated with ANCA against myeloperoxidase (MPO-ANCA). Importantly, the first genome-wide association study in GPA and MPA clearly identified that GPA and MPA are genetically distinct diseases [11]. Yet, the study also revealed that the association with identified significant single nucleotide polymorphisms (SNPs) was stronger with the ANCA type (PR3-ANCA vs. MPO-ANCA) than with the clinical syndrome questioning the classification of patients on clinical and histopathological grounds. The GWAS results are supported by several recent clinical studies demonstrating that allocation to ANCA-serotype as well as specific organ involvement may also be relevant with respect to outcome [12,13]. Apart from AAV disease type and ANCA-serotype, outcome is also influenced by intensity and duration of immunosuppressive treatment, pattern of organ involvement as well as age and gender.
Outcomes of GPA vs. MPA and PR3-ANCA vs. MPO-ANCA disease

Many studies found that GPA was more frequently associated with relapse than MPA but that death rates were higher in MPA compared to GPA [13,14]. GPA relapse rates may be attributable to ENT involvement which is known to either persist as grumbling disease or to frequently recur. Lower survival rates in MPA may be related to the proportion and severity of renal involvement which is significantly higher in MPA compared to GPA at entry diagnosis (EUVAS). Increased mortality has been associated with older as well as younger age, kidney involvement with impaired renal function, higher disease activity (as assessed by the BVAS), lower hemoglobin, higher WBC as well as MPO-ANCA [14,15].

Outcome of GPA and MPA in general has dramatically improved since the introduction of cyclophosphamide and glucocorticoids (“Fauci-scheme”). Many studies suggest that mortality rates are further decreasing since then [4,16–23]. Besides an increasing awareness for AAV, the improvement of treatment strategies seems to represent the main reason for this development. Recent studies suggest that improved outcome may be related to the curtailed used of cyclophosphamide (cyc) for remission induction and the implementation of a stringent maintenance regimen. Curtailed cyc may lead to a reduction in infection rates, hemorrhagic cystitis and cancer [17,21,22]. Treatment options are steadily widening and are mostly based on evidence from controlled trials – for nearly all disease stages [24]. The advent of biologicals in the treatment of AAV poses a new chance in further improving outcomes of AAV: Rituximab has shown equal efficacy compared to oral cyc for remission induction in generalised GPA and MPA, but it seems even superior in the treatment of subgroup of relapsing GPA/MPA patients [25]. Other reasons for improved outcome may be the technical progress in diagnostic procedures, supportive care measures (i.e., cotrimoxazole for pneumocystis prophylaxis, mesna to protect from hemorrhagic cystitis) and patient education [17,21,22]. However, short-term and long-term survival rates are still significantly reduced especially in severely diseased patients as a large analysis of EUVAS trial patients (NORAM, CYCAZAREM, MEPEX, CYCLOPS) points out [26,27]. The combined long-term analysis of four large EUVAS trials found a mortality rate of nearly 11% in the first year after diagnosis [27]. The majority of deaths were related to infection (accounting for 48% of deaths) rather than to active vasculitis (accounting for 19% of deaths) suggesting that treatment regimens need further adaptation especially with respect to glucocorticoids doses. In the long-term, a significantly elevated mortality ratio of 2.6 compared to the general population was found. After the first year of diagnosis, the major causes of death were cardiovascular disease (26%), malignancy (26%) and infection (20%) [26]. Physicians should be aware of these causes and try to minimize risk factors.

Two recent studies suggest that we need to revisit the approach of simply relating clinical phenotypes to outcome parameters: Lionaki et al. assessed outcome parameters such as relapse rate, end-stage renal disease and death in their cohort of AAV patients by allocating them via three different classification algorithms: CHCC (GPA vs. MPA), EMA (GPA vs. MPA) and ANCA-serotype (PR3-ANCA vs. MPO-ANCA) [12]. Interestingly, they found that ANCA-specificity was best at predicting relapse showing that PR3-ANCA-positive patients were nearly twice as likely to relapse compared to MPO-ANCA-positive patients. Moreover, by using a cluster analysis to identify phenotypes relevant for outcome, Mahr et al. identified five clusters within patients included in the EUVAS trials [13]: Apart from a patients group with “renal AAV and PR3-ANCA”, “renal AAV without PR3-ANCA” (mostly MPO-ANCA-positive) and “non-renal AAV”, they identified a patients group with “cardiovascular AAV” and “gastrointestinal AAV”. All of these groups had different death and relapse rates. The highest death rates were documented in the “renal AAV with PR3-ANCA” group (31.1%), closely followed by “CV AAV” and “GI AAV” groups (25.9 and 30.6%, respectively). In contrast, the “non-renal AAV” (81.0% PR3-ANCA-positive, probably representing patients with early systemic or limited disease) had the lowest death rate but the highest relapse rates (54.8%). Further studies are needed to confirm these findings, yet an increased awareness should be paid to the management of AAV in categories with adverse outcomes such as renal, CV and GI-involvement.

Outcomes of ANCA-negative GPA

ANCA-negative GPA is mainly represented by patients with localized disease (with disease manifestations restricted to the upper and lower respiratory tract and no clinical signs of vasculitis) [3,7] and by some patients with early systemic (systemic disease, no organ threatening vasculitis manifestations) [3] or limited disease (localized or early systemic patients) [28]. Patients with long-standing localized disease are rare (5% of a German monocentric cohort); nearly half of them remain ANCA-negative [7]. Patients with localized or limited disease seem to be younger at disease manifestation compared to patients with systemic disease and there is a female predominance in localized disease (72% females) [7]. Long-term survival of these groups is excellent, however, the disease course is characterized by frequent relapses (46% relapsed over a median follow-up of 48 months) and damage of the upper respiratory tract (i.e., saddle nose, perforation of sinus walls and subglottic stenosis) [7] probably reflecting that some upper respiratory tract disease manifestation may not respond to treatment as well as classic vasculitic manifestations.
Outcomes of ANCA-positive vs. ANCA-negative EGPA
Two initial studies pointed out that there are two different phenotypes in EGPA [8,9]. One phenotype is associated with ANCA (mostly MPO-ANCA) and vasculitic features such as glomerular or alveolar capillaritis whereas the other (ANCA-negative phenotype) may be associated with organ involvement resulting from eosinophilic organ infiltration such as myocarditis [8,9]. Whereas cardiac involvement has been related to adverse outcome and increased mortality before and was confirmed as the main risk factor for death in two recent studies (HR 3.37 and 2.91, respectively) [29,30], one of studies additionally found that ANCA-positive patients had a lower mortality rate but a slight increase in risk of relapse [29]. Other parameters for poor prognosis were older age at diagnosis, Five-Factor Score (FFS) and diagnosis before 1996 [29,30]. Lower eosinophil count at diagnosis was identified as being predictive of relapse [29].
In general, the outcome of EGPA has improved in a similar fashion as GPA/MPA as has been shown by two recent cohort studies [29,30]. The five-year survival rate was 91.6% for patients without cardiac involvement (and 78.2% for patients with cardiac manifestations) in the French (multicentric) Vasculitis Study Group cohort [29]. The 10-year survival rate of a German monocentric cohort was comparable (89%) with an overall SMR of 1.29 [30]. Importantly, the treatment algorithm for the German cohort using a combined strategy of glucocorticoids plus additional immunosuppressants for remission induction and maintenance and not a “glucocorticoid-only strategy” may account for the improved outcome [30]. As mentioned above, factors such as increased awareness, improved diagnostic procedures and treatment strategies as well as patient education may have an influence on the improved outcome of EGPA.

Conclusion
Outcomes of AAV have improved over the past years as has been shown by several cohort studies. Yet, early mortality rates are still high and have been linked to infections rather than to active vasculitis. Risk factors such as cardiovascular disease, malignancies and infection represent the main causes of death in the long-term. Apart from improving treatment strategies – especially in order to reduce infection rates – additional categorizations (based on ANCA-specificities and specific organ involvements) may help to identify patients at risk for adverse outcomes and to adapt treatments in a more individualized fashion.

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References


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L44. Management of relapses in vasculitis

ANCA-associated vasculitis (AAV) represents a heterogeneous group of diseases including granulomatosis with polyangitis (GPA) (formerly called Wegener’s granulomatosis), microscopic polyangitis (MPA) and Churg and Strauss syndrome [1]. AAV are conventionally treated with a strategy of remission induction using glucocorticoids combined with cyclophosphamide (CYC) followed by maintenance therapy, in order to prevent relapses. The reference maintenance treatments are azathioprine and methotrexate [2]. Very recently, the results of the MAINRITSAN study were reported, providing evidence for the superiority of maintenance rituximab treatment over azathioprine, although these results are not published yet. Despite maintenance treatment, relapses may occur in patients with AAV, which have been the object of a limited number of studies [3]. We will review treatments that can be proposed in the setting of relapsing AAV, the choice of which will be influenced by the treatments received in the past and the severity of the disease flare.

Corticosteroids

Despite the introduction of glucocorticoids into treatment strategies for vasculitis more than 50 years ago, no randomised controlled trials have been conducted to support their use. High doses of intravenous methylprednisolone, up to 3 g are proposed for severe disease flares/relapses [4]. Although they improve disease control, high-dose steroids contribute to mortality [5].

Cyclophosphamide

For sure, a combination of corticosteroids (CS) and CYC remains the standard treatment for inducing remission of GPA and MPA in patients with severe renal failure, but there is a potential risk of side effects, particularly with long-term CYC. Because intravenous CYC has been shown to be as effective as oral CYC in achieving remission of antineutrophil cytoplasm antibody (ANCA)-associated vasculitides and is less toxic, it is now widely considered an alternative to oral CYC for remission induction [6,7]. Although 75 to 90% of the patients achieve remission with oral or intravenous CYC, few data are available on therapeutic strategies for patients with disease refractory to this first-line treatment. Interestingly, oral CYC can be proposed as a rescue treatment for patients refractory to intravenous CYC. In patients newly diagnosed with systemic or renal WG or MPA with ≥ 1 poor prognosis factors, eligible in the Wegener’s Granulomatosis-Entretien (WEGENT) trial, most patients (n = 126, 79.2%) achieved remission and 32 were induction-refractory (24 GPA and 8 MPA) [2]. Induction was switched to oral CYC in 20 patients among which 15 (75%) achieved remission or low disease activity state. Alveolar haemorrhage and a creatinine level > 200 µmol/l were independently associated with induction-refractory disease [8]. Among patients with induction-refractory disease, massive alveolar haemorrhage was associated with higher mortality. Thus, switching to oral CYC can be an effective rescue treatment for patients with systemic forms of GPA or MPA who fail to achieve remission with first-line CS and intravenous CYC.