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NEPHROLOGY – REVIEW

Therapy and prognosis of ANCA-associated vasculitis from the clinical nephrologist's perspective

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Abstract This paper reviews the recently published scientific information regarding ANCA-associated vasculitis (AAV), aiming to highlight the most important data from the clinical nephrologists' perspective. The classification, pathomechanism, recent achievements of the treatment, short-term and long-term outcomes of the disease, and the difficulties nephrologists face when taking care for patients with AAV are summarized. There has been significant progress in the understanding of the genetic and pathologic background of the disease in the last years, and results of histological studies guide us to predict long-term renal function. Findings of several multicentered trials with reasonable number of participants provide comparison of the efficacy and safety of different remission induction and maintenance therapies, and evaluate recently introduced immunosuppressive agents. Although the clinical outcome of patients with AAV has improved significantly since modern immunosuppressive drugs are available, the treatment-related complications still contribute to the morbidity and mortality. To improve the survival and quality of life of patients with AAV further, knowledge of the predictors of relapse, end-stage kidney disease, and mortality, also prevention of infections and other treatment-related adverse events are important. The eligibility for renal transplantation and the option for successful pregnancies for young women are also important factors which influence the patients' quality of life. In order to provide favorable outcome, the clinicians need to establish personalized treatment strategies to optimize the intensity and minimize the toxicity of the immunosuppressive therapy.

Keywords ANCA-associated vasculitis · Rapidly progressive glomerulonephritis · Immunosuppressive therapy · Outcome · Clinical trials

Introduction

The primary systemic vasculitides are a group of diseases characterized by inflammation of the blood vessel walls. The clinical symptoms of vasculitis depend on the size and location of the involved vessels, and may vary greatly according to the degree of inflammation and consequent organ dysfunction. Most types of vasculitides are rare, and the underlying causes are poorly understood. Considering the clinical heterogeneity and the diagnostic difficulties of these complex diseases, in this paper we focus only on the antineutrophil cytoplasmic antibody (ANCA)-associated systemic small-vessel vasculitis (AAV).

Classification, pathomechanism, and presentation of AAV

ANCA-associated vasculitis is a systemic autoimmune disease that affects predominantly the small-sized blood vessels. It is a rare clinical condition with a yearly incidence rate of around 20/million population and a peak patient' age of 65–74 years. AAV is always a challenging disease causing substantial morbidity, many times life-threatening clinical condition and mortality [1–6].

In 1994, the Chapel Hill Consensus Conference established the nomenclature and definitions of small-vessel vasculitides, including microscopic polyangiitis, Wegener's

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granulomatosis characterized by granuloma formation, and Churg–Strauss syndrome, a vasculitis presenting with eosinophilia and late-onset asthma [7]. In 2012, another International Chapel Hill Consensus Conference was convened, and improved nomenclature and categorization of AAV were announced [8]. Accordingly, the major approach to small-vessel vasculitides is the types of ANCAs as myeloperoxidase-(MPO)-ANCA and proteinase3-(PR3)-ANCA. The clinicopathologic variants of AAV are the microscopic polyangiitis (MPA), the renamed granulomatosis with polyangiitis (GPA), the eosinophilic granulomatosis with polyangiitis (EGPA), and the single-organ AAV as renal-limited vasculitis.

While in GPA ANCA typically shows cytoplasmic pattern and is associated with anti-PR3 antibody formation, in MPA perinuclear ANCA with specificity for MPO is detected in most of the cases. In EGPA, the kidneys are rarely involved, and in these cases, ANCA is usually negative. However, in EGPA with necrotizing glomerulonephritis, ANCA is usually present and most often reactive to MPO. ANCA specificity may present in alternate way in a small percentage of cases [3, 9]. In single-organ renal-limited vasculitis, either types of ANCA may be present, although anti-MPO antibody is the usual phenotype [10]. Approximately 10 % of cases with pauci-immun crescentic glomerulonephritis occur with ANCA negativity [3]. In 5 % of the patients, an intriguing form of the disease develops, namely ANCA positivity presents together with anti-glomerular basement membrane antibody. On the contrary, in anti-GBM disease, up to 30 % of the affected individuals have also positive ANCA serology [11].

Etiology of AAV has not been clarified entirely, but there has been growing evidence of genetic susceptibility in the affected patients. Recently, genome-wide studies showed association with single-nucleotide polymorphisms in certain HLA regions, and interestingly different loci in the HLA region seem to be involved in the AAV subtypes [12]. Anti-proteinase3-ANCA was associated with HLA-DP and the genes encoding alpha-1 antitrypsin (SERPINA1) and proteinase3 (PRTN3), and the anti-myeloperoxidase-ANCA was associated with HLA-D9Q [13]. Environmental factors may play role as well as infections, like *Staphylococcus aureus*, certain Gram-negative bacteria and viruses, silica exposure, and perhaps ultraviolet radiation [2, 5, 14]. In the minority of patients, AAV develops secondary to drugs (propylthiouracil, hydralazine, cocaine) or autoimmune diseases (systemic lupus erythematosus, rheumatoid arthritis, systemic sclerosis, polymyositis, etc.) [5, 8].

According to AAV's major pathological pathway, local release of inflammatory cytokines primes neutrophils which express the two major target ANCA antigens, proteinase3 and myeloperoxidase on their surface [2, 15]. PR3 and MPO are proteins in the primary granules of neutrophils and lysosomes of monocytes. Activated neutrophils further release free oxygen radicals, lytic enzymes, inflammatory cytokines, complement activators, and B-cell-stimulating factors which can lead neutrophil adhesion to cytokine-activated endothelial cells through Fc receptor and Fab'2 binding, causing release of cytotoxic factors and ultimately endothelial damage. This pathologic cascade highly enhances itself, also integrates monocytes and lymphocytes into the process. The inflammation leads small-vessel necrotizing vasculitis, consecutive capillary disruption, and organ's destruction. In the glomeruli, leukocytes and inflammatory mediators enter the Bowman space and initiate glomeruli damage with crescent formation. Characteristically, the inflammation presents without any immuncomplex deposition.

Recognition of AAV is often delayed. In many times several months elapse until the correct diagnosis is established, partly due to the non-specificity of clinical symptoms, partly due to the fact that symptoms of vasculitis depend on the particular blood vessels that are involved by the inflammatory process. Beside the most prevalent constitutional complaints, such as fever, malaise, weight loss, arthralgias, and myalgias, the highly vascularized organs such as the kidneys are affected as high as 75–90 % of the patients. AAV involving the kidneys typically presents as rapidly progressive glomerulonephritis (RPGN), but it can also occur as intermittent episodes of hematuria and proteinuria due to inflammatory insults without any other clinical signs. This unrecognized subclinical glomerulonephritis might lead to glomerular scarring and interstitial fibrosis, causing advanced renal failure by the time of definite diagnosis of AAV. The upper or lower respiratory tract involvements are also frequent, and the most severe respiratory tract complication, the pulmonary hemorrhage, occurs approximately in one-third of the affected individuals. Further manifestations, such as purpura or other skin lesions, iritis or uveitis, mononeuritis multiplex or variant neurological abnormalities, gastrointestinal, and cardiac symptoms, develop less frequently, although some of them may be underrepresented in the published literature [3, 4, 6, 10, 11, 16–18].

As an international effort, the European Vasculitis Study Group (EUVAS) has organized several multicenter, international trials aiming to improve AAV's prognosis and outcome [19, 20]. EUVAS categorized AAV's patients according to the disease's extent and severity into 5 subgroups, as localized, early systemic, generalized, severe and refractory stages, in order to guide management. In addition to the EUVAS categories, disease activity can also be characterized by the Birmingham Vasculitis Activity Score (BVAS) [21]. BVAS was originally developed as a research tool in clinical trials, but it proved to be a useful predictor of survival [22, 23].

Outcome of patients in the era of modern immunosuppressive treatment

Patient survival

Before the introduction of immunosuppressive agents, 80 % of patients with systemic disease died in the first year. In the era of modern immunosuppressive therapy, survival has significantly improved, yet both the disease-associated morbidity and treatment-associated morbidity are substantial, especially in the early phase of the disease. Survival rate varies according to the severity and extent of the AAV; it has been reported between 75 and 97 % in the first year and 45–90 % in 5 years [4, 24, 25]. Patients with advanced renal failure, especially dialysis dependency, pulmonary hemorrhage, or those from higher age groups, show poorer outcome [6, 11, 26–28]. Furthermore, baseline BVAS, accompanying comorbidities and functional status, predicts long-term outcome [22, 23, 29].

Aiming to assess outcome in high number or patients, EUVAS combined data from four multicenter international trials with broad range of disease manifestations and severity [30]. In the MEPEX study (Methylprednisolone vs. Plasma Exchange as additional therapy for ANCA-associated glomerulonephritis), patients were recruited with advanced renal failure; CYCAZAREM (Cyclophosphamide vs. Azathioprine as a Remission Maintenance therapy for ANCA-associated vasculitis) and CYCLOPS (Cyclophosphamide daily Oral vs. Pulsed) trials comprised patients with mild-to moderate renal impairment; and NORAM (Non-Renal vasculitis Alternative treatment with Methotrexate) evaluated subjects with predominantly extrarenal manifestations of AAV. In this combined cohort of 524 patients with mean age of 58 years, eGFR of 39 ml/min, and BVAS of 18 at the time of diagnosis, the first-year survival was 89 %. The main causes of death were infections in the 12-month follow-up period. Those who developed adverse events, most importantly severe leucopenia due to immunosuppressive therapy and subsequent serious infections, had significantly higher first-year mortality, compared to patients without any complications. Active vasculitis accounted for only 14 %, cardiovascular disease for 13 % of mortality, and death was caused occasionally by gastrointestinal bleeding, pulmonary embolism, malignancy or other causes. Renal impairment and advance age were independently associated with occurrence of overall adverse events. Most of the deaths occurred in the first 3 months after diagnosis, when high disease activity paralleled the most intensive immunosuppressive therapy. These results highlight the importance of individualized treatment aiming to avoid or minimize immunosuppressant's' toxicity. As low GFR increased the risk of adverse events, it also underlines the utmost importance of early diagnosis.

Long-term outcome of the EUVAS recruitments showed 85 and 78 % survival at 2 and 5 years, respectively [22]. Mortality remained high in patients with AAV compared to matched general population, especially in the young age group. Causes of death after the first year of treatment were cardiovascular disease in 26 %, malignancy in 22 %, and infection in 20 %, and active vasculitis was responsible for mortality only in 8 %.

Renal survival

Renal involvement and advanced renal failure are common in AAV, up to 70 % of patients need dialysis at present [6, 28, 29]. Although dialysis can be discontinued in 20–70 % of patients when effective immunosuppressive treatment is administered, approximately one-third of survivors need long-term renal replacement therapy (RRT) [23, 24, 29]. In a smaller proportion of patients with advanced kidney failure, even end-stage kidney disease (ESKD) develops due either to a major relapse, or to ongoing inflammatory activity of AAV but in the absence of major clinical manifestations of the disease [31]. This "grumbling" feature was well documented by renal histology in 17 patients re-biopsied in clinical remission [32].

Certain renal histopathologic findings, glomerular changes, also chronic and some acute tubulointerstitial lesions, but most importantly the percentage of normal glomeruli proved to be predictors of long-term renal function [33–36]. Berden and coworkers proposed a histopathologic classification based on glomerular pathology [37]. The best renal outcome was documented in patients with focal glomerular lesions (>50 % normal glomeruli), followed by crescentic (>50 % glomeruli with cellular crescents), mixed (<50 % normal, <50 % crescentic, <50 % globally sclerotic glomeruli), and lastly sclerotic (>50 % globally sclerotic glomeruli) patterns. Patients with sclerotic lesions also had increased risk of mortality at 12 months after renal biopsy. Some subsequent studies found similar renal outcome, others documented somewhat better renal survival for the subgroup with mixed compared to crescentic glomerular pathology [36].

Importantly, immunosuppressive therapy may stabilize renal function even for patients with advanced histological changes on renal biopsy; therefore, initiation of active treatment is highly recommended. In the MEPEX trial, in spite of that the mean serum creatinine was above 500 umol/l and most of the renal biopsy findings showed extensive glomerular lesions, patients still benefited from immunosuppression accompanied with plasma exchange. This could likely be explained by the glomerular pathology which revealed predominantly acute and relatively less chronic damage [26, 36].

According to the French REIN Registry 2002–2011, and to the ERA-EDTA Registry 1993–2012, 0.7 and 1.2 %

of maintenance dialysis population developed ESKD due to AAV, respectively [38, 39]. Long-term outcome in this chronic stage of AAV was comparable to survival of non-diabetic patients on RRT, as 33 % of AAV patients were still alive at 10 years. Although the leading cause of death was of cardiovascular origin, infectious mortality occurred more frequently in subjects with AAV than in patients with other causes of renal failure. Some researchers documented similar survival, others found significantly worse, only 28 % 5 years survival of AAV patients with dialysis dependency [25, 31].

Remission and relapse

In the era of modern immunosuppression therapy, AAV has become a chronic disease characterized by periods of remission and relapses. The majority, 85–95 %, of patients undergo remission with completely absent active clinical signs of vasculitis [40, 41]. However, 30–55 % of them, after a state of remission achieved with induction immunosuppression, experience relapse in the long run [9, 40, 41]. A disease flare represents recurrence of the inflammatory activity, could be minor or major according to the presence or absence of an immediate threat to life or vital organ function, and requires repeated induction therapy with cytotoxic agents. Severe relapse has major clinical significance as it increases the overall morbidity and mortality.

According to the results of studies investigating the individual risk of relapse, patients with anti-PR3 positivity were found to have almost double likelihood of relapse than subjects with anti-MPO positivity [10]. In other investigations, which uniformly showed the elevated risk of anti-PR3 antibody positivity, relapse was predicted also by persistent ANCA positivity, mild or no renal impairment, and by cardiovascular or lung involvement [40–42]. In the EUVAS organized trials, one or more relapses occurred in 38 % of patients [42]. In patients without any risk factor, the relapse rate was 25 %, and among those with two or more risk factors, its rate increased to 59 % in 5 years. Early withdrawal of immunosuppression increases, and prolonged maintenance therapy decreases the chance for relapse, but by the cost of higher cumulative drug toxicity [24]. Importantly, according to the long-term outcome of the CYCLOPS trial, patients on oral cyclophosphamide (CYC) experienced significantly less relapse compared to those treated with intravenous (iv) bolus CYC, but the cumulative oral CYC dose was almost twice higher than the iv administered amount [43].

Relapse could occur while tapering the dose of immunosuppressants, or months or years after discontinuing them [9]. Relapse rate is lower among patients on dialysis compared to those with preserved renal function [25, 31, 44]. However, life-threatening pulmonary hemorrhage, although rarely, may occur when someone is on RRT, which advocates regular clinical monitoring and ANCA serology measurements. If severe relapse occurs, remission induction therapy has to be re-administered immediately. In minor relapses, increasing the maintenance immunosuppression may be sufficient [25].

Therapy

Remission induction

Glucocorticoid administration is a mainstay of remission induction therapy; in spite of that, the steroid's effect has never been studied in randomized controlled trials [1, 3]. In life-threatening complications as RPGN or pulmonary hemorrhage, methylprednisolone has to be given as pulse treatment in 7.5–15 mg/kg for 1–3 consecutive days, continued with daily oral administration of 1 mg/kg, up to 80 mg dose [11, 26, 45]. In less severe conditions, oral steroid treatment is sufficient for remission induction [46]. The dose of glucocorticoid needs to be tapered gradually to less than 10–20 mg/day over 3 months or by the time of remission [14].

Although steroid administration, especially pulse therapy, decreases the inflammation rapidly, monotherapy in systemic AAV, in cases with renal involvement, is unequivocally insufficient. Patients with AAV need combined immunosuppressive treatment for satisfactory long-term outcome [2, 47]. According to the EULAR/ERA-EDTA (European League Against Rheumatism/European Renal Association–European Dialysis and Transplant Association) Recommendations for the management of ANCA-associated vasculitis, published in 2016, for remission induction of organ- or life-threatening AAV, glucocorticoids with either cyclophosphamide or rituximab have to be administered [48].

Cyclophosphamide has substantially changed the course of the disease. This drug was originally introduced as continuous, oral agent in an average dose of 2 mg/kg [49]. Among the landmarking trials, CYCLOPS has demonstrated that induction with iv CYC pulses in doses between 7.5 and 15 mg/kg is as effective as the earlier recommended daily oral CYC, but with less cumulative dose and lower toxicity [50]. In that multicenter randomized controlled trial, 76 patients with renal involvement got iv CYC pulses in 2–3 weeks intervals, and their outcome was compared to the patients on daily oral CYC. Oral prednisolone was given to both groups in similar doses. CYC was administered for 3 months after achieving remission then it was switched to 2 mg/kg azathioprine (AZA) until month 18, when the study ended. Time to remission in the iv CYC-treated patients did not differ from that in the 73 controls. Nevertheless, while subjects in the pulse treatment group

got a total amount of 8.2 g, the oral CYC regimen of daily 2 mg/kg resulted in as high as 15.9 g cumulative dose. By the end of the study, GFR improved from 32 to 45 ml/min in the iv and from 29 to 45 ml/min in the oral groups; five patients died in the pulse and nine in the daily oral cohorts. When the follow-up was extended for 4.3 years, significantly more, 39.5 % of the patients on pulse treatment had relapse, compared to 20.8 % in the daily oral group [43]. In spite of more relapses among the iv-treated patients, survival and renal function did not differ between the cohorts at the end of follow-up.

The recommended dose of iv CYC by KDIGO 2012 Guideline is 0.75 g/m^2 in every 3–4 weeks, which has to be reduced to 0.5 g/m^2 for patients older than 60 years of age or with GFR less than 20 ml/min [47]. The dose has to be also lowered in case of leucopenia. The suggested oral CYC is 1.5–2.0 mg/kg, with dose adjustments similarly to the iv CYC regimen. Coadministration of mesna and generous amount of hydration prior to iv CYC therapy protect against potential severe complications such as hemorrhagic cystitis and bladder cancer, caused by the drug's toxic metabolites [51].

The beneficial role of plasma exchange (PLEX) as an adjuvant therapy in AAV has been investigated repeatedly [52]. Its theoretical effect is based on the rapid removal of ANCA antibody, inflammatory cytokines, and other circulating factors. The reasonably well-defined indications for PLEX in the course of the disease are the rapidly deteriorating advanced renal failure, the pulmonary hemorrhage and the AAV-anti-GBM glomerulonephritis overlap syndrome [3, 11, 47, 48, 53].

The MEPEX trial provided evidence of the use of PLEX for potential renal recovery, investigating 137 patients with AAV and serum creatinine >500 umol/l [26]. The efficacy of PLEX was compared to iv pulse methylprednisolone therapy. Patients were randomized to receive either seven sessions of plasma exchange over a 14-day period or 1000 mg methylprednisolone iv for three consecutive days. In addition to these therapies, all patients received prednisolone (1 mg/kg/day, tapered gradually and administered for 12 months) and oral CYC (2.5 mg/kg/day for 3 months, then 1.5 mg/kg until month 6), followed by AZA for remission maintenance. The risk of progression to ESKD at 12 months decreased by 24 % in the PLEX-treated subjects, but the patient's survival did not differ between the groups. Interestingly, the beneficial effect on renal recovery was maintained after a median of 3.95 years of follow-up, but similarly to the short-term results, PLEX did not provide long-term patient's survival advantage [54].

Other, smaller studies showed improved renal survival after PLEX therapy also in patients with moderate renal impairment [55, 56], but these results have to be confirmed in studies with higher number of participants. Such an investigation, the PEXIVAS trial (plasma exchange and glucocorticoid dosing in the treatment of antineutrophil cytoplasm antibody-associated vasculitis), has been recruiting participants, and its results are awaited in the forthcoming years [57].

Remission maintenance therapy

In the remission maintenance phase of treatment, low-dose glucocorticoid combined with another immunosuppressive medication is indicated [14, 48, 58]. Low dose means a minimum dose that is effective and safe in maintaining remission. In the meta-analysis of 13 trials including almost 1000 patients, corticosteroid administration for longer than 12 months proved to be beneficial with respect to relapse, but the optimal length of treatment could not be defined [59]. Originally, CYC was used to be administered in combination with glucocorticoid for maintenance immunosuppression over for 1 year [18]. Recognizing the long-term toxicity of CYC, recent protocols aim to decrease the exposure to this agent by changing it to other immunosuppressive drug, possessing milder side effect profile [1, 2, 47].

In the CYCAZAREM study, 144 patients (excluding subjects with severe renal failure) were randomized to either daily 2 mg/kg AZA given as soon as remission was achieved by induction with oral daily CYC in 3–6 months, or kept on oral CYC for 12 months, then switched to AZA and followed for 18 months. Low-dose corticosteroid was given to both groups. Azathioprine has been found as effective as CYC for maintenance therapy. Relapse rates were 16 and 14 % in the AZA and CYC arms, respectively [60]. Accordingly, CYC is recommended to be replaced by an alternative immunosuppressant as soon as the patients get into remission in order to reduce the total cumulative dose of CYC.

The duration of maintenance immunosuppressive treatment has not been established by randomized controlled trials. Most of the experts recommend continuous immunosuppression for 18–24 months and lifelong surveillance thereafter [14, 47, 58]. Longer maintenance therapy may be reasonable for patients with high risk of relapse. Further studies are warranted to determine when the immunosuppression can be safely discontinued.

Rituximab, the B-cell-depleting agent

Although CYC has improved the outcome of patients with AAV significantly, its relatively high toxicity urged for seeking alternative treatment options. Based on the observation that the proportion of activated B lymphocytes correlates with AAV activity, rituximab, a B-cell-depleting chimeric anti-CD20 monoclonal antibody, has become one

of the most promising novel therapeutic agents. Several trials have been organized recently to investigate its efficacy for both as remission induction and maintenance therapeutic drug [45, 61–67].

The RITUXVAS trial (Rituximab vs. cyclophosphamide in ANCA-associated vasculitis) assessed the treatment response and safety of rituximab combined with CYC as induction therapy in newly diagnosed AAV [64]. Enrolled subjects had moderate to severe renal involvement, 9 of 44 patients required RRT at diagnosis. Patients in the rituximab arm got 375 mg/m^2 rituximab weekly for four consecutive weeks combined with iv CYC on the first and third weeks; controls were treated with iv CYC for 3–6 months and then switched to azathioprine. All patients got standard glucocorticoid regimen, and plasma exchange was also permitted in severe cases. The rituximab-based therapy was not superior to iv CYC in this patient population. Median time to remission and relapse rates during the 12-month follow-up were similar in the groups, and the occurrence of adverse events, mainly infections, was also comparable. Eighteen percent of patients died in both cohorts.

Another investigation, the multicenter RAVE trial (Rituximab in ANCA-associated Vasculitis), aimed to compare the efficacy of rituximab with oral CYC in remission induction in both newly diagnosed and relapsing AAVs [61]. Eligible participants were randomized to receive either rituximab (375 mg/m^2 iv weekly for 4 weeks), or oral CYC (2 mg/kg/day, with adjustments for renal insufficiency) with a subsequent switch to AZA as soon as remission was achieved between 3 and 6 months. Both groups were also treated with glucocorticoid regimen which was aimed to be tapered off by 5 months. Rituximab proved non-inferiority to CYC, as resulted in similar complete remission rate at 6 months compared to the controls, but importantly had superior efficacy in patients with relapsing disease. Adverse event rates were similar, and quality-of-life outcomes were also comparable in the groups.

The extension of RAVE trial followed patients for 18 months [62]. Those 76 patients in the rituximab group who had achieved complete remission received only placebo during the maintenance phase, while the 70 controls in remission were switched to AZA until the end of the observation period. Between months 6 and 18, similar relapse rates, 32 and 29 %, occurred in the rituximab + placebo and the CYC + AZA-treated patients, respectively. There were no significant differences in the overall adverse events either. Interestingly, the investigators found increased risk of relapse in cases where B cells became detectable again concomitantly with rising ANCA titer in the rituximab-treated patients. This suggests that retreatment with B-cell-depleting agent is likely necessary to avoid flares. It is important to mention that although the enrolled patients had severe AAV, subjects with advanced renal failure were excluded from this study.

According to the results of these and other clinical studies, rituximab proved to be as effective as CYC to induce remission in newly diagnosed, refractory or relapsing AAV [45, 63, 65]. The EULAR/ERA-EDTA Recommendations favored rituximab over cyclophosphamide for relapsing disease, and suggested its administration also to patients with refractory AAV to cyclophosphamide [48]. The currently recommended dosage is 375 mg/m^2/infusion, given weekly for 4 weeks, or alternatively 1000 mg boluses twice in two-week interval in combination with glucocorticoids. Coadministration of CYC does not provide benefit; therefore, it is not indicated [66].

Rituximab seems to be suitable as maintenance immunosuppressive drug as well, but its optimal treatment regimen has not been determined in AAV. According to the French Vasculitis Study Group organized MAINRITSAN trial, following remission induction with corticosteroid and CYC, 500 mg doses of rituximab, given at the maintenance phase of disease on days 0 and 14 and then at months 6, 12, and 18, provided effective maintenance immunosuppression for 28 months, in comparison with daily AZA treatment administered until months 22. The rate of major relapse was significantly lower, 5 % in the rituximab group, but 29 % in the controls [67].

In a Norwegian single-center study, the efficacy of long-term rituximab therapy was retrospectively evaluated in 35 patients exclusively with GPA [63]. Beside the effectiveness of rituximab for remission induction, the investigators found that administering 2 g of rituximab annually as long-term preemptive maintenance therapy reduced the rate of relapse from 30.9 to 6.6 relapses/100 patient-years. Notably, rituximab treatment was discontinued in 37 % of the patients after a median of 41 months, mainly due to hypogammaglobulinemia and infections. Elderly subjects and those who had renal involvement had increased risk of infectious complications.

Taken together all of our current knowledge, rituximab could be the choice of drug in patients with refractory AAV, in those who had relapse or high cumulative CYC dose, for women with child-bearing potential, in immunological overlap syndromes, e.g., rheumatoid arthritis, and perhaps for patients with malignancy in their medical history [66, 68–71]. Further clinical trials are warranted to determine this agent's exact indication for remission induction in newly diagnosed patients, also to clarify the dose and length of maintenance therapy with rituximab in AAV.

Other drugs

Methotrexate has been proved to be an effective immunosuppressive agent both in induction and maintenance phase

of early systemic vasculitis without renal involvement [1, 14, 48]. As the drug is excreted by the kidneys, its administration is contraindicated if the GFR is less than 50 ml/min, so its nephrological utility is limited [2].

Mycophenolate, an effective and well-tolerated immunosuppressive agent in kidney transplantation and lupus nephritis, was investigated in AAV in the open-label randomized controlled IMPROVE trial [72]. This study compared mycophenolate to azathioprine for remission maintenance in 156 patients with moderately severe renal involvement, after remission induction with CYC and corticosteroid. Patients in the mycophenolate arm had 1.7 times more relapses than patients in the AZA arm during the 39-month follow-up. Based on these results, AZA is still the suggested first-line choice for maintenance immunosuppression, and mycophenolate is advised only for those who cannot tolerate AZA. Notably, administration of mycophenolate was found to be effective for both remission induction and maintenance in a small number of anti-MPO-positive AAV patients in a retrospective Spanish study [73]. According to an interesting observation, there is high interindividual variability in the inosine 5′-monophosphate dehydrogenase activity, which is the target enzyme for the inhibitory action of mycophenolate [74]. Furthermore, mycophenolate absorption might be hampered by certain co-medications, especially proton pump inhibitors. Both of these factors may substantially influence the immunosuppressive potency of this drug, giving some explanation to the experienced alternate effectiveness [74]. Further studies are necessary to find the exact place of mycophenolate as an immunosuppressant in AAV. The MYCYC trial is underway to assess its role in remission induction in comparison with iv CYC [20].

The efficacy of intravenous immunoglobulin (IVIG) has been documented in a small number of patients with AAV [75]. Accordingly, IVIG had beneficial, but short-term effect on the activity of the disease, as subsequent flares developed frequently on discontinuation. IVIG is mainly suggested for patients with contraindications to other immunosuppressants or as an adjuvant therapeutic agent [1, 14, 46, 48].

Treatment of subgroups with special considerations: patients on RRT and the very elderly

Immunosuppression for patients on dialysis needs serious considerations, as the infection rate and subsequent death are further increased in this population, and the risk of relapse is significantly lower than in patients with preserved renal function [25, 31, 44]. On the other hand, remission induction with iv CYC combined with corticosteroid and PLEX resulted in independent renal function at 1 year in 24 of 41 patients who required dialysis at presentation [53]. According to KDIGO 2012 Guideline, remission induction therapy accompanied by PLEX is recommended for all patients who need dialysis at diagnosis, but CYC administration is advised to discontinue at the end of third month if no renal recovery occurs, as this period is potentially sufficient enough for regaining independent renal function [47]. Patients who need long-term RRT have to be observed carefully for relapse, as extrarenal manifestations, although rarely, may become active, necessitating re-introduction of the immunosuppression.

ANCA-associated vasculitis is commonly found in elderly patients. However, clinical course of the disease in elderly, also the treatment with immunosuppressive agents are challenging, as age is independently associated with mortality in AAV, severe renal failure occurs more frequently, pulmonary hemorrhage and relapse develop comparably to younger subjects [28]. Older individuals have higher risk to develop complications to immunosuppressive drugs, especially severe infections [6]. Yet, two recent papers provided evidence that active immunosuppression prolonged dialysis-free survival in patients older than 80 years and resulted in significantly lower incidence of ESKD, compared to individuals who did not get any immunosuppression [17, 27]. Based on these data, for selected group of very elderly patients carefully calculated, individualized dose of immunosuppression is beneficial, but their conditions need careful monitoring to avoid drug-induced adverse events.

Treatment of the refractory disease and future directions

Since rituximab has been widely available, true refractoriness to treatment in AAV is rare [14, 45]. TNF-alpha blockade with infliximab might be considered as rescue therapy in these cases, but patients have to be carefully assessed due to high risk of infection [2, 46]. Gusperimus (named deoxyspergualin earlier), which is an inhibitor of the activation of nuclear factor κB, suppresses lymphocyte and macrophage function and impairs neutrophil maturation, and has proved to be effective as induction and maintenance immunosuppressive agent in AAV [76]. Alemtuzumab, a T-cell-depleting humanized monoclonal antibody against CD52, achieved remission in patients with refractory AAV, but increased the risk of infection substantially [14]. Abatacept, which inhibits T cell activation, seems promising in sustained disease control; the ABROGATE trial is going to provide more data regarding its efficacy. Another promising ongoing investigation, the CLEAR trial, with a C5a receptor inhibitor agent CCX168, aims to suppress AAV activity by influencing the alternative complement pathway [77].

Side effects of the therapy and long-term complications of the disease

High-dose glucocorticoid therapy carries the well-known risks of both short-term and long-term toxicities; thus, the modern concept of immunosuppression aims to decrease its dose and length of administration, especially in less severe, not life- or organ-threatening cases [78]. Prophylactic medications against peptic ulcer disease and osteoporosis are highly advocated [2]. Steroid-induced diabetes has to be figured on 8–10 % of cases [6, 18, 28].

CYC frequently causes leucopenia, infections, hemorrhagic cystitis, gonadal toxicity, and on long-term bladder cancer, other types of solid-organ or hematologic malignancies and myelodysplasia [6, 18, 51].

During rituximab infusion, hypersensitivity reactions with bronchospasm may develop, which has to be prevented with corticosteroid and antihistamine administration [63, 66]. Infections have been experienced with similar frequency compared to CYC [61, 68, 69]. IgG and IgM levels may decrease, and severe hypogammaglobulinemia occurs occasionally, which necessitates IVIG administration [14, 48, 63]. It is advisable to provide vaccination before initiating rituximab therapy if timing makes possible, as the drug causes diminished response to vaccines [66]. In a case series of 120 rituximab-treated patients, 13 % of late-onset neutropenia and 15 % of malignancies (non-melanoma skin, gynecologic, colon, bladder, hematologic, prostate, and renal cell cancers) developed [79].

AZA is usually well tolerated, although gastrointestinal discomfort develops frequently, which may necessitate dose reduction. Bone marrow depression and liver toxicity, on long-term lymphoproliferative disorders, need sustained awareness [2, 72].

According to the results of the four combined EUVAS trials, 66 % of patients suffered one or multiple drug-related complications [30]. Those who developed any kind of treatment-related adverse events had increased risk of poor outcome. Forty-one percent of the patients had one or multiple events of leucopenia. Agranulocytosis (<1 G/l) increased the risk of dying by 6.7 times. Infections occurred in 24 % of the patients, mostly during the first 2 months of therapy. Among the infectious agents, causing predominantly respiratory tract infections and sepsis, broad spectrum of highly pathogen or opportunistic bacteria, viruses, and fungi, sometimes parasites can also be responsible [80, 81]. Prophylaxis with trimetoprim-sulfamethoxasol decreases the incidence of Pneumocystis jiroveci infection, and furthermore reduces the rate of Staphylococci-induced respiratory tract relapse in GPA [1, 47, 48].

On the long term, occurrence of solid-organ malignancies, lymphoma, and leukemia were reported 1.6–2.4 times higher in AAV patients treated with immunosuppressive medications than that in the general population [18, 82, 83]. In the study of Westman et al. [9], 15 of 123 patients experienced malignant disease during the 994 person-years of observation between 1971 and 1993. The majority of them suffered skin cancer or urinary bladder cancer, with ten and five times higher prevalence compared to the general population, respectively. The standardized morbidity rate of vulva and testicular carcinomas was also increased, and myelodysplasia occurred in 4 subjects. Faurschou and coworkers analyzed the data of 293 patients diagnosed with GPA from the Danish National Hospital Registry between 1973 and 1999, and found substantially increased risk of non-melanoma skin cancer, late-onset urinary bladder cancer, and myeloid leukemia, especially in patients treated with more than 36 g of oral CYC [84]. Increased risk of non-melanoma skin cancer was observed from the second year, and a standardized incidence ratio (SIR) of seven was documented after 20 years of follow-up. Bladder cancer incidence was especially high in patients on high cumulative CYC dose and between 5 and 19 years of follow-up. Less than 36 g of CYC increased the risk only of non-melanoma skin cancer. According to the data of The French Vasculitis Study Group, the cumulative dose of CYC, its ever-oral administration, and the diagnosis of GPA were identified as risk factors for the fivefold increase in urinary tract malignancies in AAV patients, compared to the general population [51]. Importantly however, analyzing more recent data, the total incidence of malignancy in AAV patients has decreased, likely due to the lower cumulative dose of immunosuppressants. Follow-up of the EUVAS trials revealed 50 newly diagnosed malignancies among 535 participants during 2650 person-years. Incidence of non-melanoma skin cancers was 2.8 times higher than that in the general population, but the other types of malignancies did not show significantly elevated SIRs. Notably, this study had a relatively short 4.95 ± 3.22 years of follow-up [82]. The experienced increased risk of cancers highlights the need for long-term surveillance of late-onset malignancies in patients treated with immunosuppressive agents [51, 83]. EULAR/ERA-EDTA Recommendations call the attention to investigate persistent unexplained hematuria in patients with prior exposure to cyclophosphamide [48].

Fertility and pregnancy in patients with AAV

Cytotoxic therapies raise critical concerns regarding infertility [3, 30, 58]. CYC may result ovarian failure depending on the age of patient and the cumulative dose of the drug. In 1992, Hoffman et al. [18] published that 16 of the 28 women in reproductive age treated with GPA suffered long-term ovarian failure. Notably, in the early 90's, prolonged daily oral CYC was the preferred therapy, leading high cumulative dose of CYC. Substantially less ovarian failure

was documented a decade later in 84 women with iv bolus CYC administration for SLE, vasculitis, or other inflammatory diseases [85]. Patients got 13 ± 6.5 boluses every 3–4 weeks, with an average of 0.9 g/pulse CYC. Sustained amenorrhea occurred in 19 of them, its rate was 15.8 % when the number of pulses was seven or less, and 20 % in those who got 15 or more pulses. Importantly, all women younger than 25 years of age maintained regular cycles, but the patients who were older than 31 years had ovarian failure in 45 %, and over 40 years of age in 83 %.

Sperm production is also compromised by CYC, and azoospermia may develop, but after discontinuation of the immunosuppression, the sperm-forming cells usually recover, resulting significantly less gonadal failure in men compared to women.

In vasculitic patients with reproductive age, cytotoxic therapies are suggested to be replaced by other immunosuppressive agents, or limited cumulative dose of gonadotoxic drugs have to be considered [68, 70]. Furthermore, ovarian protection by gonadotrophic releasing hormone analogues, also sperm cryopreservation, is highly recommended [85, 86].

Pregnancy in patients with AAV is uncommon, partly due to the relatively low prevalence of this disease in young age groups, partly because of the AAV caused complications and the immunosuppressive therapy provoked infertility. In spite of these factors, case reports and small case series have been published documenting successful pregnancies in women with AAV. Of the 20 pregnancies in 12 women with systemic necrotizing vasculitis, no major relapse occurred during pregnancy or 6 months postpartum, although in 50 % of patients, mild-to-moderate vasculitic manifestations developed [87]. Three patients suffered severe complications in the third trimester as cardiac failure, pneumonia, and deteriorating renal function due to thrombotic microangiopathy. Two therapeutic abortions and 4 miscarriages occurred, 53 % of pregnancies ended prematurely, but the 14 live-borne infants were healthy. In another series of 22 pregnancies in 13 women with GPA and in one with MPA, all in remission, one vasculitic relapse developed before delivery [88]. Creatinine clearance was moderately compromised in one patient and normal in the others, and no deterioration of kidney function was experienced during pregnancy. Signs of preeclampsia presented in two women but could be stabilized by medical treatment, and no life-threatening complications occurred in the mothers. Two pregnancies ended with preterm, the outcome of babies was favorable, only one congenital malformation, a cleft palate was detected. Based on the available experiences, pregnancy should be planned when the AAV is in remission and the toxic immunosuppressants can be discontinued without significant risk of relapse. Pregnant patients have to be monitored closely by a multidisciplinary team including obstetrician (ideally, a maternal fetal medicine specialist), immunologist, nephrologists, rheumatologist, and pharmacist. In the uncommon case when a new onset AAV or disease relapse presents during pregnancy, an adequate, prompt treatment with corticosteroid, AZA, or IVIG should be administered to control the disease until delivery. Interestingly, ANCA transfers to the fetus without causing active vasculitic disease [89].

Renal transplantation

The eligibility of patients with AAV and the optimal timing of renal transplantation require serious considerations. Even earlier studies proved comparable graft survival in patients with AAV to those who underwent kidney transplantation with non-systemic inflammatory diseases [24]. In the pooled database of Nachman et al. [90] with cyclosporine-based immunosuppressive regimen, 17 % relapse was experienced in an average of 31 months from the surgery. Only 10 % of the relapses caused allograft loss. The authors emphasized that the recipients should be in remission at the time of transplantation, but they did not find any association between the circulating ANCA level at the time of surgery and the relapse rate post-transplantation.

More recently, using modern immunosuppressive agents in a series of 85 recipients with AAV, the graft and patient survival were 100 % at 1 year, and 98 and 93 % at 5 years, respectively. [91]. Eight relapses occurred in seven patients during the 64-month follow-up (range 3–165), corresponding to a relapse rate of 0.02 per patient-years. The investigators found that ANCA positivity at the time of kidney transplantation was associated with an increased risk of vasculitic relapse, regardless of the clinical remission.

Little et al. [92] reported the results of a questionnaire completed by transplant nephrologists and showed that all centers required the recipients being in remission, but they did not rely on the ANCA status. In the cohort of 107 cadaveric transplant recipients, the post-transplantation median survival was 13.4 years. Only 4.7 % of patients suffered vasculitic relapse, and the 5-year graft survival was 90 %. Importantly, an increased risk of post-transplant mortality was observed in patients for whom renal transplantation was performed earlier than 12 months after remission induction therapy.

Based on the available experiences, transplantation is feasible and should be offered to patients with ESKD and AVV, but the surgery is advised to delay as long as AAV shows activity, and performed optimally 1 year after reaching remission. Persistent ANCA positivity is not a contraindication of the surgery, but these patients need even more frequent monitoring for relapse. After transplantation

relapse of AAV may occur, however its rate is lower than the relapse rate in patients without receiving a renal graft [47, 92, 93].

Conclusion

ANCA-associated vasculitis is a rare disease carrying the prognosis from high early mortality to chronic impairments. Earlier the introduction of combined cyclophosphamide and glucocorticoid therapy dramatically improved the survival of patients with AAV. Effective control of the underlying inflammation with protocolized modern immunosuppression has further improved the overall and dialysis-free survival. Yet, challenges still remain in personalizing immunosuppressive therapy in order to avoid treatment-related serious toxicities and to improve our patients' quality of life.

Compliance with ethical standards

Conflict of interest None declared.

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