Article

ANCA-Associated Vasculitis, Anti-GBM Disease, Lupus Nephritis

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Learning Objectives

1. To identify recent advances in the use of serologic testing and histopathology for diagnosis, treatment, and prognostication in ANCA-associated vasculitis, anti-glomerular basement membrane (GBM) disease, and lupus nephritis
2. To evaluate the findings of recent controlled trials in the treatment of patients with ANCA-associated vasculitis and lupus nephritis, both for remission induction and for maintenance
3. To explain the impact of ANCA detection in patients with anti-GBM disease and lupus nephritis
4. To describe novel treatment approaches that are under investigation for immune-mediated glomerular diseases

ANCA-Associated Vasculitis

The antineutrophil cytoplasm antibody (ANCA)-associated vasculitides (AAV) are a group of rare multisystem diseases that are characterized by necrotizing inflammation of small and medium-sized blood vessels and the presence of autoantibodies to myeloperoxidase (MPO) or proteinase-3 (PR3), which are thought to play a pathogenic role (1). They include the clinical diagnoses of microscopic polyangiitis and granulomatosis with polyangiitis (2), which are frequently considered together for treatment trials, and eosinophilic granulomatosis with polyangiitis, which we do not discuss here. Clinical presentation can vary widely, although renal involvement with pauci-immune glomerulonephritis is common (>80%).

There have been dramatic improvements in patient outcome over the past 50 years, and survival is now estimated to be >90% at 1 year. This is due, at least in part, to the findings of many successful therapeutic trials in AAV, and the resultant publication of several consensus treatment guidelines (which we will not review in detail) (3–5). It is recognized, however, that therapy-related toxicities—including infection, cardiovascular disease, and malignancy—are now the leading causes of morbidity and mortality in patients with AAV. Thus, recent studies have aimed to (*1*) improve diagnostics and identify biomarkers that will allow earlier and personalized treatment, (*2*) refine treatment regimens for acute disease to avoid drug toxicity, and (*3*) prevent the accrual of damage associated with flare and its retreatment, by improving remission-maintenance therapies, such that adverse events may be avoided and long-term outcomes improved.

Diagnostic and Prognostic Biomarkers

An updated consensus statement on ANCA testing in vasculitis was published in 2017 (6). This recognizes the many technical innovations in ANCA detection since the first consensus, and the improved sensitivity and specificity of newer antigen-specific assays. It recommends their first-line use in patients with suspected vasculitis. Indirect immunofluorescence is no longer recommended as a screening tool; in patients where there is a high degree of clinical suspicion and a negative antigen-specific test result (or conversely where there is a weak, possibly false, positive test result), a second antigen-specific assay should be used to improve sensitivity and specificity. The consensus recognizes that AAV cannot be ruled out in ANCA-negative cases (occurring in approximately 10% of patients with a clinical diagnosis of microscopic polyangiitis or granulomatosis with polyangiitis) in whom histologic diagnosis should be pursued. A consensus statement of ANCA testing beyond systemic vasculitis was recently published (7).

The pursuit of better biomarkers in AAV has been a major research focus, although few have progressed to clinical application. CD163 is a cell-surface protein shed by activated macrophages and monocytes; its detection in the urine (likely derived from glomerular leukocytes) can differentiate patients with active renal vasculitis from those in remission, and those with other forms of acute kidney injury (8). It can be detected, at generally lower levels, in patients with other forms of glomerular disease, indicating that it may not be specific for AAV, although it may identify glomerular involvement in patients with a known diagnosis of systemic vasculitis. A recent study showed that combining sCD163 with other urinary markers (monocyte chemoattractive protein-1 [MCP-1], proteinuria) could increase the likelihood of detecting milder renal disease in AAV (9). At least one recent trial included urinary biomarkers as a secondary end point, and a validated ELISA for urinary sCD163 is now commercially available in Europe, although it is not yet clear whether this assay will be taken up in clinical practice.

Whereas urinary biomarkers may provide a noninvasive alternative to renal biopsy for identifying glomerulonephritis, they do not provide additional prognostic information. A histopathologic classification for ANCA-associated glomerulonephritis was proposed in

2010, which distinguished four classes of disease based on the pattern of glomerular injury, and which predicted long-term renal outcome, with increasing severity of kidney function loss in focal (>50% normal glomeruli), crescentic (>50% cellular crescents), mixed (<50% normal glomeruli with no predominant lesion), and sclerotic class disease (>50% globally sclerosed glomeruli) (10). There was disagreement, however, in independent validation studies on the outcome in patients with crescentic and mixed disease, so the classification was recently revisited by the original investigators in a large, international, multicenter cohort of 145 new patients with long-term follow-up (11). This confirmed best and worst renal outcomes in focal and sclerotic class disease, respectively, but in contrast to the original study, rates of end-stage kidney disease (ESKD) at 10 years were not significantly different between crescentic and mixed disease: 14% versus 20% (P=0.98). The investigators noted that crescentic disease usually presented with lower eGFR values, which tended to improve over time toward eGFR values like those in mixed disease, suggesting that crescentic class disease may be more responsive to immunosuppressive treatment.

An alternative renal risk score that incorporates both histopathologic (% normal glomeruli, % interstitial fibrosis and tubular atrophy) with clinical parameters (eGFR at diagnosis) was recently developed in patient cohorts from Germany (12). The score stratified patients at low, medium, or high risk of ESKD at 36 months, which occurred in 0%, 26% to 27%, and 68% to 78% of cases, respectively. These findings have been confirmed in a small number of independent validation studies, although overall rates of ESKD were lower when the renal risk score was applied to the international cohort (n=145) used in the new histopathologic classification study. This was attributed in part to differences in treatment between cohorts.

A common finding of these prediction tools is that the proportion of normal glomeruli in the kidney biopsy specimen is a strong predictor of long-term outcome. However, neither scoring scheme has fully addressed the impact of treatment on outcome prediction, and although they provide some additional prognostic formation, they currently lack enough accuracy to guide decisions on treatment intensification or withdrawal.

Recent Clinical Studies of Remission Induction Therapy

Current guidelines recommend that, for remission-induction in patients with severe disease, including those with pauci-immune glomerulonephritis, treatment should be with high-dose glucocorticoids and either rituximab or cyclophosphamide (3–5). In patients with rapidly progressive glomerulonephritis (RPGN) or lung hemorrhage, consideration of plasma exchange has been recommended. The optimum dose, route of administration, and duration of cyclophosphamide treatment have been well studied; pulsed intravenous regimens are equivalent to daily oral treatment for initial disease control and are associated with lower incidence of adverse events such as leukopenia, though at the potential cost of increased relapse risk during long-term follow-up (13,14). Two randomized controlled trials have shown noninferiority of rituximab to cyclophosphamide for remission induction (15,16), so the past decade has seen its increasing use, either as first-line therapy or as an alternative in those who are intolerant or resistant to cyclophosphamide. However, the controlled trials failed to show a reduction in adverse events with rituximab, so recent studies have aimed to (*1*) identify alternative induction agents (*e.g.,* mycophenolate mofetil [MMF]), (*2*) reduce glucocorticoid exposure (*e.g.,* with complement inhibition), and (*3*) improve renal outcomes (*e.g.,* with plasma exchange), given the impact of ESKD on overall outcome.

Mycophenolate Mofetil

Two recent trials have investigated the use of MMF for remission induction in acute disease. MYCYC (Clinical Trial of Mycophenolate Versus Cyclophosphamide in ANCA Vasculitis) was a noninferiority study that compared 3–6 months of treatment with MMF (2–3 g/day) to pulsed intravenous cyclophosphamide (15 mg/kg, 6–10 doses), followed by azathioprine maintenance in all cases (17). The trial recruited 140 patients with newly diagnosed disease (60% PR3-ANCA positive), most of whom had renal involvement (81%), although severe renal impairment (eGFR <15 ml/min) was an exclusion criterion. MYCYC confirmed noninferiority of MMF for its primary end point of remission at 6 months with adherence to a protocolized glucocorticoid taper: 67% in the MMF group versus 61% in the cyclophosphamide group (risk difference, 5.7%; 90% confidence interval [90% CI], –7.5% to 19%]). However, relapse was more common after induction with MMF: 33% versus 19% (incidence rate ratio 1.97; 95% CI, 0.96 to 4.23; P=0.049), and there was no difference in the rate of serious infection with either treatment. Indeed, there were numerically more infections in MMF-treated patients: 26% versus 17% (odds ratio [OR], 1.67; 95% CI, 0.68 to 4.19). Although this was not a statistically significant difference, the underlying hypothesis that MMF is less toxic than cyclophosphamide seems disproven, although the use of high-dose glucocorticoids in both groups (approximately 6 g) may have contributed to these infection rates, highlighting the need to refine glucocorticoid regimens in AAV.

Another study explored the use of MMF for re-induction of remission in patients presenting with their first or second disease relapse (in contrast to MYCYC, which exclusively recruited newly diagnosed cases) (18). As such, it included a greater proportion of patients with PR3-ANCA positivity (81% of the total 84 cases). Like MYCYC, it excluded patients with severe renal dysfunction (serum creatinine >5.66 mg/dl or new dialysis dependence). Patients were randomized to receive either MMF (2 g/day) or oral cyclophosphamide (2 mg/kg per day) for 6 months, at which point all were switched to azathioprine maintenance therapy. In keeping with the findings of MYCYC, there was no difference in the primary end point of remission at 6 months: 66% with MMF versus 81% with cyclophosphamide (P=0.11), a trend toward more frequent relapse after MMF: 61% versus 43% at 2 years (P=0.10), and no evidence of reduced infections with MMF (42% versus 41%). A *post hoc* exploratory analysis showed that MMF induced remission in a similar proportion of patients as cyclophosphamide in those with lower disease activity (*i.e.,* Birmingham Vasculitis Activity Score [BVAS] <19).

Thus, whereas these studies do not identify a routine role for MMF for remission induction in new or relapsing AAV, they provide evidence for an alternative treatment option for patients with mild disease, or at low risk of relapse (*e.g.,* MPO-ANCA positive), who wish to avoid cyclophosphamide exposure (owing to intolerance or concerns for fertility or other toxicities related to cumulative

cyclophosphamide dose), particularly in resource-poor settings where access to biologic therapies such as rituximab may be limited.

Plasma Exchange

The use of plasma exchange for treatment of RPGN was first described in the 1970s, and there have since been several small observational and controlled studies in AAV. A meta-analysis in 2011 and a Cochrane review in 2019 considered these studies and concluded that plasma exchange may reduce the rate of ESKD but that the overall quality of the evidence was low (19,20). The paucity of strong evidence for plasma exchange, and the need for studies in patients with moderately severe renal involvement, led to the development of PEXIVAS (Plasma Exchange and Glucocorticoid Dosing in the Treatment of AAV).

PEXIVAS was the largest randomized trial in AAV to date. It recruited >700 patients with moderate to severe renal impairment (eGFR <50 ml/min; no lower limit) who were randomized in a 2 × 2 factorial design to receive (*1*) either plasma exchange or no plasma exchange and (*2*) a standard versus a reduced dose glucocorticoid taper (approximately 3.2 g versus approximately 1.8 g oral glucocorticoids in the first 3 months) after induction therapy with intravenous glucocorticoids (1–3 g) and either rituximab or cyclophosphamide (followed by azathioprine maintenance in the latter) (21). During median follow-up of 2.9 years, plasma exchange did not have a significant impact on the composite primary outcome of ESKD or death (hazard ratio [HR], 0.86; 95% CI, 0.65 to 1.13; *P*=0.27). Nor were there differences in secondary outcomes, including death (HR, 0.87; 95% CI, 0.58 to 1.29), ESKD (HR, 0.81; 95% CI, 0.57 to 1.13), or serious infection (HR, 1.21; 95% CI, 0.96 to 1.52). There was no interaction with glucocorticoid assignment, and these results were similar across subgroups stratified for age, ANCA serotype, severity of renal disease, presence of lung hemorrhage, and choice of induction immunosuppression (rituximab in 15% and oral or intravenous cyclophosphamide in 85%). It was anticipated that plasma exchange may have particular benefit during early follow-up, although the results remained similar when censored for analysis at 12 months. These findings are compelling; this was a large trial that included patients from >90 centers in 16 countries, which, along with the broad enrollment criteria, provides generalizable results. Numbers lost to follow-up were small, and assigned treatment adherence was good, despite the open-label design. The findings indicate that plasma exchange should not be used routinely during remission induction therapy, particularly in those with milder disease presentations. It may have a place in the treatment of refractory disease, or in patients with contraindications to other components of therapy, inasmuch as there were trends toward benefit in some subgroups (*e.g.,* severe lung hemorrhage) and no signal of harm from plasma exchange in the trial.

Glucocorticoids

The second question addressed by PEXIVAS related to glucocorticoid dosing; the reduced-dose regimen was shown to be noninferior with respect to the primary outcome of ESKD or death (absolute risk difference, 2.3% 95% CI, –4.5 to 9.1), with significantly fewer serious infections in the first year in the reduced-dose group (incidence rate ratio, 0.69; 95% CI, 0.52 to 0.93]). There were no other differences in secondary end points, and the results were broadly similar across the predefined subgroups, although there was a trend toward higher rates of ESKD in patients who received rituximab and, low-dose steroids, that may warrant further examination (HR, 1.86; 95% CI, 0.83 to 4.14). This was the first study to compare initial glucocorticoid regimens in a controlled fashion, and we expect that the low-dose taper will be rapidly adopted in clinical practice.

A reduced-dose glucocorticoid regimen is non-inferior to traditional regimens for remission-induction with respect to death or ESKD, and results in fewer infections.

Several recent studies have sought to reduce glucocorticoid exposure further. One suggested approach has been to combine rituximab with low-dose cyclophosphamide to ensure rapid disease control, thus enabling the use of lower glucocorticoid doses during remission induction. Single-center cohort studies suggest that this approach is safe and effective with either a short course of oral cyclophosphamide or a low-dose intravenous regimen (akin to the Eurolopus protocol) (22,23). This combination approach also formed the basis of a very rapid glucocorticoid taper assessed in a prospective open-label cohort study from two centers in the United Kingdom; 49 patients with renal AAV were treated with a combination induction of rituximab (total 2 g), low-dose cyclophosphamide (approximately 3 g), and a short course of glucocorticoids of 1 to 2 weeks duration (total intravenous and oral dose approximately 1.2 g) (24). Two patients required early reintroduction of glucocorticoids for treatment of active disease during the first 6 months, although all remaining patients achieved disease remission by this time point, which was accompanied by improvements in C-reactive protein, renal function, and proteinuria. At 12 months, 90% of patients were in sustained remission. A case-control analysis with two groups of matched patients enrolled in previous EUVAS trials, which used standard glucocorticoid dosing, showed comparable remission rates and improvements in eGFR during the first year but with lower incidence of new-onset diabetes (0% versus 8%) and severe infections (12% versus 30%, *P*=0.02). These preliminary results are promising, but this was a small study of patients with nonsevere kidney disease (median serum creatinine 2 mg/dl), of whom the majority (67%) were MPO-ANCA positive and thus at low risk of relapse, and for a limited period of 1 year of follow-up. Given that early withdrawal of glucocorticoids has been associated with an increased risk of relapse beyond 12 months (25), long-term follow-up of subgroups at greater risk of relapse treated with this regimen in a controlled study are needed.

Complement Inhibition

Complement inhibition has emerged as a potential route to glucocorticoid avoidance in AAV. Historically regarded as a pauci-immune vasculitis, without detectable complement deposition on the biopsy specimen, a critical role for the alternate complement pathway in disease pathogenesis has emerged over the past decade (26). Avacopan is a small molecule inhibitor of the C5a receptor that was first shown to be effective in an experimental model of MPO-AAV in mice transgenic for the human C5aR. It was subsequently tested in a phase 2 clinical study (CLEAR; Safety and Efficacy of CCX168 in

Subjects With AAV) that enrolled 67 patients with active AAV with nonsevere renal involvement (eGFR >20 ml/min) (27). Patients were treated with rituximab or cyclophosphamide and randomized to receive placebo plus prednisone starting at 60 mg daily (control group, *n*=23), avacopan plus reduced-dose prednisone (20 mg daily, *n*=22), or avacopan without prednisone (*n*=22). The study had a 12-week follow up period, and the primary efficacy measure was the proportion of patients achieving a ≥50% reduction in BVAS at this point, with no worsening in any body system. This was achieved in 70%, 86%, and 81% of control, reduced-prednisolone, and no-prednisolone patients, respectively ($P<0.002$ for noninferiority, for both intervention groups compared with control). There were corresponding improvements in secondary end points, including comparable changes in eGFR and absolute BVAS, and better improvements in albuminuria, urinary MCP-1, and quality of life scores, in avacopan-treated patients. The overall rate of adverse events was comparable across the three treatment groups, but there were fewer side effects related to glucocorticoid use (such as new-onset diabetes, psychiatric disorders, and weight gain) in the avacopan treatment groups compared with control. This trial used a novel stepwise design (rather than a concurrent parallel group randomization) to gather preliminary evidence for the safety and efficacy of avacopan that enabled the bold move to entirely eliminate glucocorticoids from the induction regimen in the final step. As such, the results of this study garnered significant attention, although confirmation of these findings in larger randomized controlled trials is needed; the trial was small and of short duration, it excluded patients with severe renal disease, and the primary efficacy end point (>50% reduction in BVAS) is of questionable validity in the practical care of patients with AAV. A phase 3 study of avacopan (ADVOCATE, NCT02994927) completed recruitment in 2018, and results are expected soon.

Remission Maintenance Therapy

In patients with severe AAV who are in remission after treatment with high-dose glucocorticoids and cyclophosphamide or rituximab, the traditional approach to remission maintenance was with an extended treatment period of 12–18 months with low-dose glucocorticoids and an additional immunosuppressive agent (3–5). After cyclophosphamide-based remission induction, a switch to azathioprine maintenance at 3–6 months is equivalent to continued treatment with cyclophosphamide for 1 year and is superior to MMF (28,29). Thus, until recently, azathioprine tended to be used as first-line maintenance treatment in patients with renal disease (in whom methotrexate may be contraindicated because of impaired GFR).

Duration of Maintenance Therapy

The duration of maintenance therapy with conventional oral immunosuppressants was addressed in the REMAIN (Randomized Controlled Trial of Prolonged Treatment in the Remission Phase of AAV) study (30). It included patients (*n*=117; 96% after first presentation) with either MPO- or PR3-AAV, who were in remission with cyclophosphamide-based induction treatment, and compared maintenance therapy with azathioprine and prednisolone for a period of 24 versus 48 months. Relapse was more frequent with shorter treatment: 62% versus 22% (HR, 2.84; 95% CI, 1.72 to 4.9), which may have accounted for a higher incidence of ESKD seen in this group (7.8% versus 0%, $P=0.012$). ANCA positivity at randomization was associated with subsequent relapse risk (51% versus 29% if ANCA negative (OR, 2.57; 95% CI, 1.16 to 5.68; $P=0.017$), perhaps consistent with recent literature that reasserts a role for ANCA as a biomarker to guide treatment. There were numerically more adverse events with prolonged treatment (43 versus 28, $P=0.07$), of which nine and three, respectively ($P=0.13$), were serious, although there were no differences in damage accrual (as determined by Vasculitis Damage Index) or overall patient survival (91.5% versus 96.1%). However, the study was underpowered to detect significant differences in adverse outcomes. This trial, perhaps unsurprisingly, demonstrates that extended treatment may prevent relapse in AAV, although with the potential risk of more adverse events. This may be justified in patients with greater risk of relapse (*e.g.,* ANCA positive at switch to maintenance treatment) or in whom the stakes of relapse are highest (*e.g.,* those with impaired kidney function at risk of progression to ESKD). Whether these findings are relevant in the rituximab-based remission maintenance era is not known.

Rituximab for Remission Maintenance

MAINRITSAN (Rituximab versus Azathioprine to Maintain Remission in AAV), conducted by the French Vasculitis Study Group (FVSG), was the first controlled study of rituximab for remission maintenance. It was a moderately sized trial (*n*=115) that compared azathioprine (starting dose 2 mg/kg per day) with regular rituximab infusions (500 mg every 6 months) after induction with pulsed intravenous cyclophosphamide, for a total follow-up period of 28 months (31). Rituximab was remarkably effective in maintaining remission, and clearly superior to azathioprine treatment; only 3 of 57 (5%) patients in the rituximab group experienced major relapse by month 28, compared with 17 of 58 (29%) with azathioprine (HR, 6.61; 95% CI, 1.56 to 27.96; $P=0.002$). There was no difference in adverse events (25 in each group), including serious infection (8 versus 11 with azathioprine and rituximab, respectively) or cancer (2 versus 1, respectively). Glucocorticoid dosing was not protocolized in this study, but patients were taking moderately high doses of prednisolone at the initiation of maintenance therapy (16 mg daily). Although no statistically significant differences in glucocorticoid use between groups were observed, their potential contribution to maintaining disease control should be considered. Long-term follow-up of this study was published in 2018; patients were followed up prospectively for a total of 60 months from enrollment, without further treatment after month 28 (32). At month 60, major relapse-free survival was 49.5% versus 71.9% in the azathioprine and rituximab groups, respectively (HR for relapse, 2.51; 95% CI, 1.35 to 4.69; $P=0.003$). Cumulative glucocorticoid use, immunoglobulin levels, and the rate of adverse events, including infection, were not different between groups. Thus, whereas the incidence of relapses increased in both groups after treatment cessation at month 28, there appeared to be a sustained benefit of rituximab for remission maintenance during long-term follow-up.

It was observed during long-term follow-up in MAINRITSAN that nearly all patients who experienced relapse after rituximab treatment were ANCA positive and/or had repopulation of circulating CD19+ B cells at the time of flare. A second trial by the FVSG, MAINRITSAN2, asked whether these biomarkers could be used to tailor timing of rituximab retreatment during remission maintenance (33). A control group received the rituximab regimen established in

the first MAINRITSAN study (*i.e.,* regular 500-mg infusions every 6 months), whereas the intervention group received 500-mg infusions only when circulating CD19+ B cells were detectable (>0 cells/μl) or after changes in ANCA titer (from negative to positive serostatus, or doubling of titer on antigen-specific assay). The primary end point was the number of relapses at month 28. This was a larger trial (n=162) that enrolled patients in remission after induction treatment with either cyclophosphamide (in 62%) or rituximab (in 38%) along with glucocorticoids. Whereas there were numerically more relapses in the tailored dosing group, this was not statistically significant (14/81 [17.3%] versus 8/81 [9.9%], P=0.22), and relapse-free survival was comparable between groups (83.3% versus 86.4%, P=0.58). Major relapse with either treatment approach was very infrequent (7.4% versus 3.7%, P=0.23). There was no difference in cumulative glucocorticoid use or the incidence of adverse events, although numerically fewer infections were reported in the tailored dosing group (11.1% versus 19.8% in the fixed group). There was also a difference in the number of administered rituximab infusions; overall, the tailored group received 248 infusions versus 381 in the fixed group, with a median of 3 (interquartile range [IQR] 2–4) versus 5 (IQR 5–5) doses per patient, respectively.

These findings suggest that immunologic biomarkers may be used to guide rituximab retreatment, and they are consistent with a recent report that changes in PR3-ANCA in particular may predict flare after rituximab (34). Indeed, it should be emphasized that the majority of patients in both MAINRITSAN studies were PR3-ANCA positive and/or had a clinical diagnosis of granulomatosis with polyangiitis, so whether maintenance rituximab is necessary, justified, or cost effective in patients with a lower risk of relapse (*e.g., de novo* presentations of MPO-ANCA disease) is unknown. The clear message of both studies, however, is that rituximab-based regimens are more effective than conventional oral immunosuppressants for maintaining remission, although the preferred dosing regimen is debated: tailored dosing guided by biomarkers may be as efficacious, more cost effective, and potentially safer than fixed-dosing schedules, although this approach is contingent on regular monitoring of immunologic markers (performed every 3 months in the study), which may not be readily available at all centers. In addition, it is recognized that relapses can occur in the absence of detectable circulating ANCA or B cells. On this basis, recent expert consensus guidelines from the United Kingdom recommend that, when used for remission-maintenance, rituximab (500–1000 mg) should be administered at fixed 6-monthly intervals and that further investigation is needed to define the role of biomarkers to guide treatment (35).

Regular rituximab infusions are superior to conventional oral immunosuppressants for remission maintenance in AAV, and optimum dosing schedules are under investigation.

To this end, the MAINTANCAVAS study (Maintenance of AAV Remission by Intermittent Rituximab Dosing; NCT02749292) is investigating remission maintenance with rituximab, with the aim of determining whether redosing by B cell reconstitution or return of ANCA is more effective. Finally, the RITAZAREM trial (Rituximab versus Azathioprine as Maintenance Therapy in Relapsing AAV; NCT01697267) studied rituximab for maintenance in patients with relapsing disease (in contrast to MAINRITSAN1 and 2, which included a high proportion of patients with new-onset disease). Recruitment was completed in 2016, and results are expected this year.

Outcomes

Although there have been considerable improvements in outcome for patients with AAV over the past 40 years, they remain at increased risk of death compared with age- and sex-matched controls. A recent North American study identified 484 patients with diagnoses of AAV between 2002 and 2017 who had a standardized mortality ratio of 2.3 (95% CI, 1.9 to 2.8) (36). The standardized mortality ratios for infection and renal disease were most significantly elevated: 13.9 (95% CI, 7.9 to 24.5) and 4.3 (95% CI, 1.6 to 11), respectively. During a mean follow-up period of 7.1 (±4.1) years, the leading causes of death were cardiovascular disease (cumulative incidence 7.1%), malignancy (5.9%) and infection (4.1). These findings are compatible with those of a previous meta-analysis and data from EUVAS studies (37,38), although with the benefit of derivation from a contemporary cohort, in a nontrial setting, in whom a significant proportion of patients received treatment with modern immunosuppressive regimens (39% received rituximab as initial disease therapy). These findings indicate that there is significant need to further reduce drug toxicity and to attend to the long-term cardiovascular risk of patients with AAV.

The treatment and outcome in elderly patients with AAV presents an additional challenge. It is notable that the average age of patients recruited to the induction therapy trials discussed above was between 57 and 63 years, and it is not clear that their findings are generalizable to older patients, who represent an increasing proportion of those encountered in clinical practice. Two recent studies have examined the outcomes in elderly patients in more detail. The first included 83 patients of median age 75 (range, 65–92) who were treated at a tertiary center in the United Kingdom (39). All patients received immunosuppressive treatment (rituximab in 37%, cyclophosphamide in 39%, MMF in 12%; with adjunctive plasma exchange in 27% and glucocorticoids in 96%). Of note, only one patient received intravenous glucocorticoids, and the average total dose of prednisolone received during the first 3 months was relatively low, at approximately 2 g. Although the study lacked a control group, the 2- and 5-year survival appeared favorable at 83% (75%–92%) and 75% (65%–86%), respectively. Baseline frailty, as defined by the Rockwood Clinical Frailty Score, was associated with poorer outcome.

A second observational study from Japan included 167 patients with median age 77 years (40). In contrast to the first study, 100 patients were treated with glucocorticoids alone, without additional immunosuppression (cyclophosphamide was the most used agent in the remainder). During mean follow-up of 28 months (range, 0–166), 36 patients (21.3%) died, and the cumulative proportions of survival at 1, 3, and 5 years were 89% (95% CI, 79% to 90%), 84% (95% CI, 77% to 89%), and 74% (95% CI, 64% to 82%), respectively. The most frequent cause of death was infection. Logistic regression analysis showed that initial high-dose corticosteroid administration: prednisolone ≥0.8 mg/kg per day (OR, 3.86; 95% CI, 1.14 to 13.10; P=0.03) and serum creatinine ≥1.5 mg/dL at diagnosis (OR, 5.13; 955 CI, 1.75 to 15.0; P=0.003) were independent

predictors of early severe infection, although administration of cyclophosphamide or rituximab was not (OR, 1.76; 95% CI, 0.57 to 5.4; *P*=0.322).

Taken together, these studies indicate that elderly patients can do well after immunosuppressive treatment for AAV, compatible with prior reports (41). The suggestion that intravenous / high-dose glucocorticoids should be avoided in elderly patients requires prospective evaluation, and it underscores the need to include older individuals in controlled trials, perhaps stratified for some of the associations with poorer outcome identified here (*e.g.,* formal frailty score).

Anti-GBM Disease

Anti-GBM disease is a small vessel vasculitis that usually presents with RPGN, diffuse alveolar hemorrhage, or both. It serves as a model autoimmune kidney disease, being characterized by the presence of directly pathogenic autoantibodies directed against well-characterized antigens in the NC1 domains of collagen IV in the glomerular and alveolar basement membranes. As such, the disease has been extensively studied and recently reviewed elsewhere (42). Here, we discuss recent clinical developments and experimental findings that may have implications for the care of patients with this condition.

Epidemiology and Genetics

Anti-GBM disease is one of the rarest forms of glomerulonephritis; a nationwide study in Ireland defined an incidence of 1.6 cases per million per year, and it is likely that the disease has comparable frequency in other European populations (43). Precise epidemiologic data in non-Europeans are lacking, although anti-GBM disease is well recognized in Asian populations and is thought to be rare in those of African descent. The Irish study is notable for demonstrating substantial regional variability in disease incidence, and for identifying both temporal and spatial clustering of cases. This finding confirms prior anecdotal reports of disease "outbreaks," and suggests that environmental exposures, such as infection, may have an important role in triggering disease onset in susceptible individuals. In keeping with this suggestion, prodromal infections were a common finding in a large cohort of Chinese patients with anti-GBM disease, reportedly affecting 93 of 140 patients (47% were lower respiratory tract, and 31% were upper respiratory tract) although without any consistent causative organism (44). A recent case series described a cluster of cases occurring in association with the outbreak of the novel coronavirus, SARS-CoV-2 (45). The molecular mechanisms that underlie these associations with infection are not defined, although processes of molecular mimicry and idiotype-anti-idiotype interactions have been invoked in experimental rodent models.

A series of elegant studies in murine models has likewise shed light on the mechanisms of HLA-linked susceptibility to anti-GBM disease. Inheritance of HLA-DR15 is consistently associated with disease susceptibility, whereas HLR-DR1, -DR7, and -DR9 are negatively associated with disease risk. Indeed, HLA-DR1 and -DR7 appear to confer a dominant negative protective effect if coinherited with HLA-DR15. Studies in mice transgenic for human HLA molecules (and lacking murine MHC class 2) confirms these epidemiologic observations: HLA-DR15 transgenic mice are susceptible to induction of experimental anti-GBM disease, whereas mice transgenic for either HLA-DR1 or both HLA-DR15 and DR1 are resistant (46,47). These studies suggest that presentation of the immunodominant T cell epitope in the distinct binding registries of HLA-DR15 and -DR1 can differentially induce conventional and tolerogenic T cell responses, respectively, thus accounting for the dominant protective effect of HLA-DR1 via induction of antigen-specific regulatory T cells, even when coinherited with the HLA-DR15 susceptibility allele. This novel finding in an archetypal autoimmune disease may have broad relevance in several forms of HLA-linked autoimmunity.

Treatment and Outcomes

Current treatment guidelines recommend that in patients with alveolar hemorrhage or crescentic glomerulonephritis with <100% crescents on the kidney biopsy specimen, anti-GBM disease should be treated with plasma exchange, cytotoxic immunosuppression, and glucocorticoids (3). Given the rarity of the disease, there is a paucity of controlled data for the efficacy of this treatment regimen, although observational studies show that it is effective when initiated before the onset of anuric and/or dialysis-dependent renal failure (42). Several recent retrospective studies provide further evidence for this approach and provide predictors of treatment response and outcome.

A large multicenter analysis from the French Society of Hemapheresis assessed the outcomes in 122 patients who were all treated with plasma exchange (along with cyclophosphamide and/or glucocorticoids in the majority) (48). Most patients had severe disease; 78% presented with pulmonary-renal syndrome, the median creatinine at presentation was 7 mg/dl, and more than two thirds required dialysis as part of their initial treatment. Despite the severity of disease at diagnosis, overall patient survival at 1 year was favorable at 87%, although it should be noted that the study cohort was atypical in its age distribution (median age, 31 years; only 22% of patients >60 years at diagnosis). Indeed, in multivariable analysis, age >60 years and the number of delivered plasma exchanges correlated with overall survival (HR, 16.1; 95% CI, 3.4 to 76.6; and HR, 0.87; 95% CI, 0.77 to 0.98, respectively). Specifically, a cutoff of eight plasma exchange sessions was associated with positive and negative predictive survival rates of 95% and 47%, respectively. A trend toward improved survival with oral versus intravenous cyclophosphamide did not achieve statistical significance in multivariable analysis (HR, 0.14; 95% CI, 0.02 to 1.37; *P*=0.09), although this observation suggests the optimum route and dose of cyclophosphamide requires further study in anti-GBM disease, inasmuch as controlled evidence in the treatment of AAV (which suggests therapeutic equivalence of oral and intravenous cyclophosphamide, with fewer adverse events with the latter) may not translate to anti-GBM disease. Renal outcome in this study was less favorable; 38% of surviving patients had independent kidney function at 12 months. Only serum creatinine >5.6 mg/dl at diagnosis was predictive of dialysis dependence at this timepoint (HR, 16.2; 95% CI, 3.96 to 67.9) in multivariable analysis.

A second, distinct, French study of 119 patients aimed to further define predictors of long-term prognosis (49). This cohort was older than in the former study (median age, 54 years), although the severity of kidney disease at presentation was comparable; patients had median creatinine of 7.2 mg/dl, and 78% required initial dialysis

treatment. Plasma exchange was used in >80%, and the majority also received immunosuppression with cyclophosphamide (82%) and/or rituximab (9%). Overall survival at 1 year and 5 years was 95% and 92%, respectively. In this study, increasing age (HR for 10 years, 4.1 95% CI, 1.89 to 8.88), requirement for mechanical ventilation (HR, 5.1; 955 CI, 1.02 to 26.4), and the presence of cardiovascular risk factors, including hypertension (HR, 19.9; 95% CI, 2.52 to 157.2) and dyslipidemia (HR, 11.1; 95% CI, 2.71 to 45), were negatively associated with overall survival. As in the former study, the use of plasma exchange was associated with better outcome (HR, 0.29; 95% CI, 0.08 to 0.98), although the potential for confounding by indication may account for this finding, inasmuch as plasma exchange may have been withheld in patients with adverse prognostic factors in whom aggressive treatment was deemed futile. Unadjusted predictors of renal survival at 3 months included age and severity of renal disease at presentation (as determined by serum creatinine or need for initial dialysis). Pulmonary involvement (whether determined by presenting features or by need for mechanical ventilation) was associated with better renal survival, perhaps owing to earlier diagnosis or more aggressive treatment in those presenting with systemic features. It should be noted that a significant proportion of patients (23%) were lost to follow-up for renal evaluation at early time points in this study.

In both French studies, recovery from early dialysis dependence was infrequent (2.4% and 16%, respectively), a finding common to nearly all studies in anti-GBM disease. Indeed, the KDIGO guidelines recognize that in the absence of lung hemorrhage, when 100% of glomeruli on the kidney biopsy specimen are affected by crescent formation, recovery from dialysis is so unlikely that treatment may be considered futile (3). A recent international multicenter study of 123 patients with biopsy-proven anti-GBM glomerulonephritis aimed to identify better histopathologic predictors of renal survival, to guide treatment decisions (50). Overall 5-year renal survival in this study was 34%, and it confirmed that patients with 100% crescents on the biopsy specimen did not recover renal function if they were dialysis dependent at presentation. In addition, patients with sclerotic class disease (>50% of glomeruli affected by global sclerosis) did not recover, so aggressive treatment may also be considered futile in these cases. In multivariable analysis, dialysis dependency at presentation (HR, 3.17; 95% CI, 1.59 to 6.32), percentage of normal glomeruli (HR, 0.97; 95% CI, 0.95 to 0.99), and extent of interstitial infiltrate in the kidney biopsy specimen (HR 2.02, 95% CI, 1.17 to 3.50) were predictors of ESKD during follow-up. We note, however, that there are isolated reports of renal recovery in patients presenting with these adverse histologic features, and we emphasize that decisions to withhold treatment require careful consideration of both clinical and pathologic findings.

The poor kidney outcome in patients presenting with dialysis-dependent renal failure highlights the need for more rapid and effective treatments in anti-GBM disease. IdeS, the immunoglobulin G degrading enzyme of *Streptococcus pyogenes*, is one potential new agent. IdeS is an endopeptidase that enables microbial evasion of the host immune response by rapidly cleaving all IgG subclasses at the hinge region into F(ab')2 and Fc fragments. Recent studies have aimed to exploit this unique activity for the treatment of antibody-mediated diseases, including anti-GBM disease. In a murine model of anti-GBM disease, IdeS treatment reduced glomerular inflammatory cell infiltration and albuminuria (51). Treatment was notable for cleaving GBM-bound IgG, thus affecting noncirculating antibodies that may possibly be inaccessible to plasma exchange. In a preliminary clinical study of three patients, a single dose of IdeS was remarkably efficient at clearing circulating and tissue-bound anti-GBM antibodies, although rebound of circulating IgG occurred after approximately 1 week in all patients, and none recovered kidney function (52). However, this proof-of-concept study specifically recruited patients with refractory disease and adverse prognostic factors; future studies should aim to address whether IdeS will have a role in supplementing or replacing plasma exchange in the routine treatment of anti-GBM disease.

"Double-Positive" ANCA and Anti-GBM Disease

The coexistence of antineutrophil cytoplasm antibodies (ANCA) in patients with anti-GBM disease is well recognized. In most series, 30%–50% of patients have detectable ANCA, usually recognizing MPO. Previous studies have reported variable findings in these double-positive cases, with some suggesting they have favorable outcome compared with isolated anti-GBM disease, and others indicating equivalent or poorer outcome. A recent multicenter European study compared the clinical features and long-term outcomes in 37 double-positive patients with parallel cohorts of single-positive anti-GBM disease (n=41) and AAV (n=568) (53). The double-positive patients had the severe disease features of anti-GBM at presentation, with high rates of alveolar hemorrhage (38%) and dialysis-dependent renal failure (57%). However, a nonstatistical trend toward recovery from dialysis was observed in the double-positive patients compared with single-positive anti-GBM patients (33% versus 17%), perhaps indicating varied mechanisms of kidney injury. In addition, during long-term follow-up (median 4.8 years), patients with double-positive disease experienced relapse at a frequency comparable with those with AAV, whereas no single-positive anti-GBM patients experienced relapse. These findings indicate a hybrid disease phenotype that displays key features of both anti-GBM disease and AAV.

Patients "double positive" for ANCA and anti-GBM antibodies exhibit the severe disease manifestations of anti-GBM at presentation, but carry the long-term relapse risk of AAV.

The mechanism of this association between ANCA and anti-GBM disease is not defined, although the finding that double-positive patients have the age distribution of AAV patients, with prodromal symptoms and more chronic lesions on renal biopsy specimens (findings more typical of AAV), might suggest that AAV is the initial pathologic state that triggers the onset of anti-GBM disease by disrupting the quaternary structure of the GBM, thus releasing sequestered epitopes to immune detection.

It was also recently suggested that antiperoxidasin antibodies may account for some of the ANCA reactivity detected in patients with anti-GBM disease (54). Peroxidasin is a member of the heme peroxidase family, which shares some sequence homology to MPO. It is essential for the formation of basement membranes, and in particular for the generation of the quaternary structure that confers immune privilege to the pathogenic epitopes in type 4 collagen in

anti-GBM disease. Circulating autoantibodies to peroxidasin were found in 11 of 24 patients at diagnosis with anti-GBM disease, and their development may predate onset of clinical manifestations. These antibodies were shown to cross-react to MPO, and in a separate cohort of patients with MPO-AAV, specific antibodies to peroxidasin were also identified, where they correlated with more severe disease features. The authors speculate that antibodies to peroxidasin may therefore have pathogenic potential in a range of pulmonary renal syndromes, although further work is required to fully characterize their clinical significance.

Lupus Nephritis

Systemic lupus erythematosus (SLE) is a chronic autoimmune disease, which can affect any organ, but lupus nephritis is one of the more common (approximately 60%) and severe manifestations, and it accounts for much of the morbidity and mortality of lupus. SLE is considerably more common in women than men, at a ratio of 6 to 13: 1, across all age groups. The disease is characterized by autoimmunity to nuclear components, including anti-ds DNA antibodies, and also by antibodies against complement components such as C1Q. The mortality of SLE has fallen over the past 30 years with the introduction of better immunosuppressive treatment, including intravenous cyclophosphamide and MMF, and more recently the development of ESKD was also reported to have reduced. There are now several consensus recommendations for managing SLE (3,55–57), and the topic of lupus nephritis has been well reviewed recently (58,59), so this article will focus on selected clinical developments.

Epidemiology

Epidemiologic studies show considerable variation in the incidence of SLE and of lupus nephritis in different parts of the world and in different ethnic groups. In the United States, SLE has a higher incidence and prevalence in Blacks and Hispanics than in Whites. In a number of reports, the incidence in Blacks ranges from around 8–16/100,000 person-years, compared with 3–6 in Whites (60). A recent study of 724 patients shows increased prevalence of lupus nephritis in Blacks, Asian/Pacific Islanders, and Hispanics, with prevalence ratios of 1.74 (95%, 1.40 to 2.16), 1.68 (95%, 1.38 to 2.05), and 1.35 (95%, 1.05 to 1.74), respectively, compared with the White population (61). The time to development of nephritis after diagnosis of SLE was also shorter in the ethnic minority groups, with the highest risk in the first year after diagnosis. There have also been changes in the clinical presentation of lupus nephritis over the past five decades, as shown in a study of 499 patients from Italy (62). The authors reported a progressive increase in patient age at the time of diagnosis, a longer time between diagnosis of SLE and development of lupus nephritis, and a progressive increase in presentation with urinary abnormalities rather than renal insufficiency. The survival without ESKD ranged from 87% at 10 years in the earliest 15-year period to 99% in the most recent period. These observations suggest that the presentation of lupus nephritis has become less severe in recent years, perhaps as a result of improved diagnosis, and that this may contribute to improvements in long-term outcome.

Histology

Lupus nephritis can be classified into six histologic classes, from 1 to 6, according to the recommendations of the International Society of Nephrology/Renal Pathology Society. This classification has been of value in guiding treatment and also in developing clinical trials. A recent revision of the classification provides new and clearer definitions for mesangial and endocapillary proliferation and for crescents (63). The previous class 4-S and 4-G lesions have been eliminated, and a new proposal has been made for activity and chronicity indices, based on the National Institutes for Health scoring system. The evaluation of these proposed definitions is ongoing.

The relationship between clinical disease activity and histologic activity is not clear and has been questioned in recent studies. In one study, 28 patients with proliferative lupus nephritis underwent repeated biopsy after treatment, and it was found that about a third of patients with a clinical response still had high histologic activity and that two thirds of patients in histologic remission were still clinically active (64). Evidence of chronicity at the second biopsy was associated with development of CKD. In a second study, 36 patients treated for proliferative lupus nephritis and in remission for 12 months underwent repeated kidney biopsy before tapering immunosuppression (65). Flares of lupus nephritis occurred almost exclusively in those with histologic activity on the second biopsy specimen, suggesting that repeated kidney biopsy may be useful in managing maintenance immunosuppression.

Associated Antibodies

It is well recognized that patients with lupus nephritis may sometimes have positive test results for ANCA, but the clinical relevance of this has been unclear. A recent study demonstrated positivity for ANCA in 29 (17%) patients with lupus nephritis, and of these 82% had anti-MPO antibodies (66). Patients positive for ANCA were more likely to have class 4-S nephritis and glomerular necrosis and had a tendency toward more crescents. They also had more severe renal impairment at the time of biopsy and were more likely to receive cyclophosphamide, but they had no significant difference in outcome. It therefore seems likely that in at least some patients, the ANCA are contributing to the glomerular pathologic changes.

Since the discovery of anti-PLA2R antibodies in primary membranous nephropathy, it has consistently been found that patients with class 5 (membranous) lupus nephritis are negative for these antibodies. However, a recent study demonstrated the presence of antibodies to exostocin (EXT) 1 and 2 in approximately 10% of patients with anti-PLA2R-negative membranous nephropathy, including eight of 18 with class 5 lupus nephritis (67). The clinical importance of this finding is not yet clear. Please see the article on membranous nephropathy in this issue of nephSAP for additional discussion.

Surrogate End Points

There has been intense clinical trial activity in lupus nephritis over recent years, including studies showing the effectiveness of MMF and of low-dose intravenous cyclophosphamide, both in combination with corticosteroids. Given that the major goal in treatment of lupus nephritis is preservation of kidney function, the early studies depended on end points such as doubling of serum creatinine or developing ESKD. To allow analysis of the effects of treatment at earlier time points, a recent study assessed the role of hazard index tools, including 12-month proteinuria and 12-month serum creatinine, using a database of almost 1000 patients with lupus nephritis (68). Both of these hazard index tools correlated well with long-term

kidney outcomes, so they should be considered as surrogate end points for clinical trials.

Multitarget Therapy

Recent clinical trials have studied the use of multitarget therapy, with the addition of calcineurin inhibitors to standard therapy, and of a variety of biologic agents in lupus nephritis. A large multicenter study of 368 patients from China compared induction therapy with a combination of tacrolimus (4 mg/day), MMF (1 g/day), to intravenous cyclophosphamide (0.75 g/m^2 per month) (69). Both groups received intravenous and oral glucocorticoids. At 24 weeks, 45.9% of patients in the multitarget group had achieved complete remission, compared with 25.6% in the intravenous cyclophosphamide group (P<0.001). The overall (complete and partial) response rate was also higher in the multitarget group (83.5% versus 63.0%, P<0.001), in whom the time to remission was approximately 4 weeks shorter. In a follow-up study of patients who had responded at 24 weeks (n=206), the multitarget therapy group continued using the same combination (tacrolimus 2–3 mg/day, MMF 0.5–0.75g/day) and the intravenous cyclophosphamide group were switched to azathioprine (2 mg/kg per day), both with oral prednisolone (10 mg/day). At 18 months, the multitarget group showed a comparable renal relapse rate (5.47% versus 7.62%, P=0.74) and fewer adverse events (16.4% versus 44.4%, P<0.01) (70). These findings supported the investigators' hypothesis that targeting multiple aspects of the immune response could be more effective than single-agent therapy and that lower doses of multiple drugs may maximize efficacy and minimize adverse effects.

This hypothesis was further tested in an ethnically diverse patient population with class 3, 4, or 5 nephritis in the international phase 2 AURA-LV study (n=265). Voclosporin, a next-generation calcineurin inhibitor, was compared at high-dose (39.5 mg twice daily) and low-dose (23.7 mg twice daily) to placebo treatment, in addition to therapy with MMF (2 g/day) and a rapidly tapered course of oral glucocorticoids for remission induction (71). Patients receiving voclosporin showed a higher complete remission rate than controls: high dose 27.3%, low dose 32.6%, placebo 19.3% (OR for low dose, 2.03; 95% CI, 1.01 to 4.05; P=0.46) at 24 weeks, which was maintained at 48 weeks in the low-dose group (39.%, 49.4%, 23.9%, respectively). There were adverse events related to treatment in voclosporin groups, though this was driven in part by the protocolized need to assess changes in eGFR, which, not surprisingly, occurred more frequently in CNI-treated patients. These changes were generally reversible, and within 2 weeks of the study conclusion, mean eGFR levels returned to baseline in all groups. However, infections were more common (13.6% high dose, 12.4% low dose, 8.0% placebo), as were serious adverse events (25.0%, 28.1%, 15.9%) in voclosporin-treated patients. A phase 3 trial of voclosporin as a component of multitarget therapy completed recruitment in 2019, and results are expected soon (AURORA; Aurinia Renal Response in Active Lupus with Voclosporin; NCT03021499)

Rituximab

The use of rituximab, a monoclonal antibody that depletes CD20+ B cells, appears a logical approach to treatment of SLE that is supported by several observational studies (72). However, the LUNAR (Lupus Nephritis Assessment with Rituximab) study of 144 patients failed to show additional benefit of rituximab over placebo in lupus nephritis, when added to MMF and glucocorticoids (73). In that trial, B cell depletion was defined as CD19+ count <20 cells/μl. When the results were reanalyzed defining B cell depletion as 0 cells/μl, it was found that complete peripheral depletion of B cells, and the rapidity and duration of depletion, were associated with a complete response at week 78 (unadjusted OR of complete response after peripheral depletion 5.8. 95% CI, 1.2 to 28; P=0.03) (74). This interesting result suggests that rituximab may be effective in lupus nephritis provided there is adequate B cell depletion. Additional evidence comes from an observational study which found that rituximab alone or with low-dose steroids was effective in treating 13 of 15 patients with pure class 5 lupus nephritis, with a median time to remission of 5 months (75). Belimumab, a monoclonal antibody against B cell activating factor (BAFF) has been shown to be effective in SLE, although not specifically in lupus nephritis. Because of the known rebound in BAFF levels after rituximab, which could lead to repopulation of autoreactive B cells, the combination of belimumab and rituximab is being investigated. In one phase 2 study of patients with refractory disease, this combination prevented the post–rituximab surge in BAFF, reduced neutrophil extracellular trap formation, allowed reduction in immunosuppression in 14 of 16 patients, and led to renal responses in 11 patients (76). Further research on this interesting approach is warranted.

References

1. Jennette JC, Falk RJ: Pathogenesis of antineutrophil cytoplasmic autoantibody-mediated disease. *Nat Rev Rheumatol* 10: 463–473, 2014 PubMed
2. Jennette JC: Overview of the 2012 revised International Chapel Hill Consensus Conference nomenclature of vasculitides. *Clin Exp Nephrol* 17: 603–606, 2013 PubMed
3. Kidney Disease: Improving Global Outcomes (KDIGO) Glomerulonephritis Work Group. KDIGO clinical practice guideline for glomerulonephritis. Available at: https://kdigo.org/guidelines/gn/. Accessed October 6, 2020
4. Ntatsaki E, Carruthers D, Chakravarty K, D'Cruz D,L, Jayne D, et al.; BSR and BHPR Standards, Guidelines and Audit Working Group: BSR and BHPR guideline for the management of adults with ANCA-associated vasculitis. *Rheumatology (Oxford)* 53: 2306–2309, 2014 PubMed
5. Yates M, Watts RA, Bajema IM, Cid MC, Crestani B, Hauser T, et al.: EULAR/ERA-EDTA recommendations for the management of ANCA-associated vasculitis. *Ann Rheum Dis* 75: 1583–1594, 2016 PubMed
6. Bossuyt X, Cohen Tervaert JW, Arimura Y, Blockmans D, Flores-Suárez LF, Guillevin L, et al.: Position paper: Revised 2017 international consensus on testing of ANCAs in granulomatosis with polyangiitis and microscopic polyangiitis. *Nat Rev Rheumatol* 13: 683–692, 2017 PubMed
7. Moiseev S, Cohen Tervaert JW, Arimura Y, Bogdanos DP, Csernok E, Damoiseaux J, et al.: 2020 international consensus on ANCA testing beyond systemic vasculitis. *Autoimmun Rev* 19: 102618, 2020 PubMed
8. O'Reilly VP, Wong L, Kennedy C, Elliot LA, O'Meachair S, Coughlan AM, et al.: Urinary soluble CD163 in active renal vasculitis. *J Am Soc Nephrol* 27: 2906–2916, 2016 PubMed
9. Moran SM, Monach PA, Zgaga L, Cuthbertson D, Carette S, Khalidi NA, et al.: Urinary soluble CD163 and monocyte chemoattractant protein-1 in the identification of subtle renal flare in anti-neutrophil cytoplasmic antibody-associated vasculitis. *Nephrol Dial Transplant* 35: 283–291, 2020 PubMed
10. Berden AE, Ferrario F, Hagen EC, Jayne DR, Jennette JC, Joh K, et al.: Histopathologic classification of ANCA-associated glomerulonephritis. *J Am Soc Nephrol* 21: 1628–1636, 2010 PubMed
11. van Daalen EE, Wester Trejo MAC, Göçeroğlu A, Ferrario F, Joh K, Noël LH, et al.: Developments in the histopathological classification of ANCA-associated glomerulonephritis. *Clin J Am Soc Nephrol* 15: 1103–1111, 2020 PubMed

12. Brix SR, Noriega M, Tennstedt P, Vettorazzi E, Busch M, Nitschke M, et al.: Development and validation of a renal risk score in ANCA-associated glomerulonephritis. *Kidney Int* 94: 1177–1188, 2018 PubMed
13. De Groot K, Rasmussen N, Bacon PA, Tervaert JW, Feighery C, Gregorini G, et al.: Randomized trial of cyclophosphamide versus methotrexate for induction of remission in early systemic antineutrophil cytoplasmic antibody-associated vasculitis. *Arthritis Rheum* 52: 2461–2469, 2005 PubMed
14. Harper L, Morgan MD, Walsh M, Hoglund P, Westman K, Flossmann O, et al.; EUVAS investigators: Pulse versus daily oral cyclophosphamide for induction of remission in ANCA-associated vasculitis: Long-term follow-up. *Ann Rheum Dis* 71: 955–960, 2012 PubMed
15. Stone JH, Merkel PA, Spiera R, Seo P, Langford CA, Hoffman GS, et al.; RAVE-ITN Research Group: Rituximab versus cyclophosphamide for ANCA-associated vasculitis. *N Engl J Med* 363: 221–232, 2010 PubMed
16. Jones RB, Tervaert JW, Hauser T, Luqmani R, Morgan MD, Peh CA, et al.; European Vasculitis Study Group: Rituximab versus cyclophosphamide in ANCA-associated renal vasculitis. *N Engl J Med* 363: 211–220, 2010 PubMed
17. Jones RB, Hiemstra TF, Ballarin J, Blockmans DE, Brogan P, Bruchfeld A, et al.; European Vasculitis Study Group (EUVAS): Mycophenolate mofetil versus cyclophosphamide for remission induction in ANCA-associated vasculitis: A randomised, non-inferiority trial. *Ann Rheum Dis* 78: 399–405, 2019 PubMed
18. Tuin J, Stassen PM, Bogdan DI, Broekroelofs J, van Paassen P, Cohen Tervaert JW, et al.: Mycophenolate mofetil versus cyclophosphamide for the induction of remission in nonlife-threatening relapses of antineutrophil cytoplasmic antibody-associated vasculitis: Randomized, controlled trial. *Clin J Am Soc Nephrol* 14: 1021–1028, 2019 PubMed
19. Walsh M, Catapano F, Szpirt W, Thorlund K, Bruchfeld A, Guillevin L, et al.: Plasma exchange for renal vasculitis and idiopathic rapidly progressive glomerulonephritis: A meta-analysis. *Am J Kidney Dis* 57: 566–574, 2011 PubMed
20. Walters GD, Willis NS, Cooper TE, Craig JC: Interventions for renal vasculitis in adults. *Cochrane Database Syst Rev* 1: CD003232, 2020 PubMed
21. Walsh M, Merkel PA, Peh CA, Szpirt WM, Puéchal X, Fujimoto S, et al.; PEXIVAS Investigators: Plasma exchange and glucocorticoids in severe ANCA-associated vasculitis. *N Engl J Med* 382: 622–631, 2020 PubMed
22. Cortazar FB, Muhsin SA, Pendergraft WF 3rd, Wallace ZS, Dunbar C, Laliberte K, et al.: Combination therapy with rituximab and cyclophosphamide for remission induction in ANCA vasculitis. *Kidney Int Rep* 3: 394–402, 2017 PubMed
23. McAdoo SP, Medjeral-Thomas N, Gopaluni S, Tanna A, Mansfield N, Galliford J, et al.: Long-term follow-up of a combined rituximab and cyclophosphamide regimen in renal anti-neutrophil cytoplasm antibody-associated vasculitis. *Nephrol Dial Transplant* 34: 63–73, 2019 PubMed
24. Pepper RJ, McAdoo SP, Moran SM, Kelly D, Scott J, Hamour S, et al.: A novel glucocorticoid-free maintenance regimen for anti-neutrophil cytoplasm antibody-associated vasculitis. *Rheumatology (Oxford)* 58: 260–268, 2019 PubMed
25. Walsh M, Merkel PA, Mahr A, Jayne D: Effects of duration of glucocorticoid therapy on relapse rate in antineutrophil cytoplasmic antibody-associated vasculitis: A meta-analysis. *Arthritis Care Res (Hoboken)* 62: 1166–1173, 2010 PubMed
26. Chen M, Jayne DRW, Zhao MH: Complement in ANCA-associated vasculitis: mechanisms and implications for management. *Nat Rev Nephrol* 13: 359–367, 2017 PubMed
27. Jayne DRW, Bruchfeld AN, Harper L, Schaier M, Venning MC, Hamilton P, et al.; CLEAR Study Group: Randomized trial of C5a receptor inhibitor avacopan in ANCA-associated vasculitis. *J Am Soc Nephrol* 28: 2756–2767, 2017 PubMed
28. Jayne D, Rasmussen N, Andrassy K, Bacon P, Tervaert JW, Dadoniené J, et al.; European Vasculitis Study Group: A randomized trial of maintenance therapy for vasculitis associated with antineutrophil cytoplasmic autoantibodies. *N Engl J Med* 349: 36–44, 2003 PubMed
29. Hiemstra TF, Walsh M, Mahr A, Savage CO, de Groot K, Harper L, et al.; European Vasculitis Study Group (EUVAS): Mycophenolate mofetil vs azathioprine for remission maintenance in antineutrophil cytoplasmic antibody-associated vasculitis: A randomized controlled trial. *JAMA* 304: 2381–2388, 2010 PubMed
30. Karras A, Pagnoux C, Haubitz M, Groot K, Puechal X, Tervaert JWC, et al.; European Vasculitis Society: Randomised controlled trial of prolonged treatment in the remission phase of ANCA-associated vasculitis. *Ann Rheum Dis* 76: 1662–1668, 2017 PubMed
31. Guillevin L, Pagnoux C, Karras A, Khouatra C, Aumaître O, Cohen P, et al.; French Vasculitis Study Group: Rituximab versus azathioprine for maintenance in ANCA-associated vasculitis. *N Engl J Med* 371: 1771–1780, 2014 PubMed
32. Terrier B, Pagnoux C, Perrodeau É, Karras A, Khouatra C, Aumaître O, et al.; French Vasculitis Study Group: Long-term efficacy of remission-maintenance regimens for ANCA-associated vasculitides. *Ann Rheum Dis* 77: 1150–1156, 2018 PubMed
33. Charles P, Terrier B, Perrodeau É, Cohen P, Faguer S, Huart A, et al.; French Vasculitis Study Group: Comparison of individually tailored versus fixed-schedule rituximab regimen to maintain ANCA-associated vasculitis remission: Results of a multicentre, randomised controlled, phase III trial (MAINRITSAN2). *Ann Rheum Dis* 77: 1143–1149, 2018 PubMed
34. van Dam LS, Dirikgil E, Bredewold EW, Ray A, Bakker JA, van Kooten C, et al.: Proteinase-3-anti-neutrophil cytoplasmic antibodies (PR3-ANCAs) predict relapses in ANCA-associated vasculitis patients after rituximab [published online ahead of print June 30, 2020]. *Nephrol Dial Transplant* doi: 10.1093/ndt/gfaa066.2020 PubMed
35. Tieu J, Smith R, Basu N, Brogan P, D'Cruz D, Dhaun N, et al.: Rituximab for maintenance of remission in ANCA-associated vasculitis: Expert consensus guidelines. *Rheumatology (Oxford)* 59: e24–e32, 2020 PubMed
36. Wallace ZS, Fu X, Harkness T, Stone JH, Zhang Y, Choi H: All-cause and cause-specific mortality in ANCA-associated vasculitis: Overall and according to ANCA type. *Rheumatology (Oxford)* 59: 2308–2315, 2020 PubMed
37. Tan JA, Dehghan N, Chen W, Xie H, Esdaile JM, Avina-Zubieta JA: Mortality in ANCA-associated vasculitis: A meta-analysis of observational studies. *Ann Rheum Dis* 76: 1566–1574, 2017 PubMed
38. Flossmann O, Berden A, de Groot K, Hagen C, Harper L, Heijl C, et al.; European Vasculitis Study Group: Long-term patient survival in ANCA-associated vasculitis. *Ann Rheum Dis* 70: 488–494, 2011 PubMed
39. McGovern D, Williams SP, Parsons K, Farrah TE, Gallacher PJ, Miller-Hodges E, et al.: Long-term outcomes in elderly patients with ANCA-associated vasculitis. *Rheumatology (Oxford)* 59: 1076–1083, 2020 PubMed
40. Waki D, Nishimura K, Tokumasu H, Kadoba K, Mukoyama H, Saito R, et al.: Initial high-dose corticosteroids and renal impairment are risk factors for early severe infections in elderly patients with antineutrophil cytoplasmic autoantibody-associated vasculitis: A retrospective observational study. *Medicine (Baltimore)* 99: e19173, 2020 PubMed
41. Weiner M, Goh SM, Mohammad AJ, Hruskova Z, Tanna A, Bruchfeld A, et al.: Outcome and treatment of elderly patients with ANCA-associated vasculitis. *Clin J Am Soc Nephrol* 10: 1128–1135, 2015 PubMed
42. McAdoo SP, Pusey CD: Anti-glomerular basement membrane disease. *Clin J Am Soc Nephrol* 12: 1162–1172, 2017 PubMed
43. Canney M, O'Hara PV, McEvoy CM, Medani S, Connaught DM, Abdalla AA, et al.: Spatial and temporal clustering of anti-glomerular basement membrane disease. *Clin J Am Soc Nephrol* 11: 1392–1399, 2016 PubMed
44. Gu QH, Xie LJ, Jia XY, Ma R, Liao YH, Cue Z, et al.: Fever and prodromal infections in anti-glomerular basement membrane disease. *Nephrology (Carlton)* 23: 476–482, 018 PubMed
45. Prendecki M, Clarke C, Cairns T, Cook T, Roufosse C, Thomas D, et al.: Anti-glomerular basement membrane disease during the COVID-19 pandemic. *Kidney Int* 98: 780–781, 2020 PubMed
46. Ooi JD, Chang J, O'Sullivan KM, Pedchenko V, Hudson BG, Vandenbark AA, et al.: The HLA-DRB1*15:01-restricted Goodpasture's T cell epitope induces GN. *J Am Soc Nephrol* 24: 419–431, 2013 PubMed
47. Ooi JD, Petersen J, Tan YH, Huynh M, Willett ZJ, Ramarathinam SH, et al.: Dominant protection from HLA-linked autoimmunity by antigen-specific regulatory T cells. *Nature* 545: 243–247, 2017 PubMed

48. Huart A, Josse AG, Chauveau D, Korach JM, Heshmati F, Bauvin E, et al.; French Society of Hemapheresis: Outcomes of patients with Goodpasture syndrome: A nationwide cohort-based study from the French Society of Hemapheresis. *J Autoimmun* 73: 24–29, 2016 PubMed
49. Marques C, Carvelli J, Biard L, Faguer S, Provôt F, Matignon M, et al.: Prognostic factors in anti-glomerular basement membrane disease: A multicenter study of 119 patients. *Front Immunol* 10: 1665, 2019 PubMed
50. van Daalen EE, Jennette JC, McAdoo SP, Pusey CD, Alba MA, Poulton CJ, et al.: Predicting outcome in patients with anti-GBM glomerulonephritis. *Clin J Am Soc Nephrol* 13: 63–72, 2018 PubMed
51. Yang R, Otten MA, Hellmark T, Collin M, Björck L, Zhao MH, et al.: Successful treatment of experimental glomerulonephritis with IdeS and EndoS, IgG-degrading streptococcal enzymes. *Nephrol Dial Transplant* 25: 2479–2486, 2010 PubMed
52. Soveri I, Mölne J, Uhlin F, Nilsson T, Kjellman C, Sonesson E, et al.: The IgG-degrading enzyme of Streptococcus pyogenes causes rapid clearance of anti-glomerular basement membrane antibodies in patients with refractory anti-glomerular basement membrane disease. *Kidney Int* 96: 1234–1238, 2019 PubMed
53. McAdoo SP, Tanna A, Hrušková Z, Holm L, Weiner M, Arulkumaran N, et al.: Patients double-seropositive for ANCA and anti-GBM antibodies have varied renal survival, frequency of relapse, and outcomes compared to single-seropositive patients. *Kidney Int* 92: 693–702, 2017 PubMed
54. McCall AS, Bhave G, Pedchenko V, Hess J, Free M, Little DJ, et al.: Inhibitory anti-peroxidasin antibodies in pulmonary-renal syndromes. *J Am Soc Nephrol* 29: 2619–2625, 2018 PubMed
55. Hahn BH, McMahon MA, Wilkinson A, Wallace WD, Daikh DI, Fitzgerald JD, et al.; American College of Rheumatology: American College of Rheumatology guidelines for screening, treatment, and management of lupus nephritis. *Arthritis Care Res (Hoboken)* 64: 797–808, 2012 PubMed
56. Gordon C, Amissah-Arthur MB, Gayed M, Brown S, Bruce IN, D'Cruz D, et al.; British Society for Rheumatology Standards, Audit and Guidelines Working Group: The British Society for Rheumatology guideline for the management of systemic lupus erythematosus in adults. *Rheumatology (Oxford)* 57: e1–e45, 2018 PubMed
57. Fanouriakis A, Kostopoulou M, Cheema K, Anders HJ, Aringer M, Bajema I, et al.: 2019 Update of the Joint European League Against Rheumatism and European Renal Association-European Dialysis and Transplant Association (EULAR/ERA-EDTA) recommendations for the management of lupus nephritis. *Ann Rheum Dis* 79: 713–723, 2020 PubMed
58. Almaani S, Meara A, Rovin BH: Update on lupus nephritis. *Clin J Am Soc Nephrol* 12: 825–835, 2017 PubMed
59. Anders HJ, Saxena R, Zhao MH, Parodis I, Salmon JE, Mohan C: Lupus nephritis. *Nat Rev Dis Primers* 6: 7, 2020 PubMed
60. Stojan G, Petri M: Epidemiology of systemic lupus erythematosus: An update. *Curr Opin Rheumatol* 30: 144–150, 2018 PubMed
61. Maningding E, Dall'Era M, Trupin L, Murphy LB, Yazdany J. Racial and ethnic differences in the prevalence and time to onset of manifestations of systemic lupus erythematosus: The California Lupus Surveillance Project. *Arthritis Care Res (Hoboken)* 72: 622–629, 2020 PubMed
62. Moroni G, Vercelloni PG, Quaglini S, Gatto M, Gianfreda D, Sacchi L, et al.: Changing patterns in clinical-histological presentation and renal outcome over the last five decades in a cohort of 499 patients with lupus nephritis. *Ann Rheum Dis* 77: 1318–1325, 2018 PubMed
63. Bajema IM, Wilhelmus S, Alpers CE, Bruijn JA, Colvin RB, Cook HT, et al.: Revision of the International Society of Nephrology/Renal Pathology Society classification for lupus nephritis: Clarification of definitions, and modified National Institutes of Health activity and chronicity indices. *Kidney Int* 93: 789–796, 2018 PubMed
64. Malvar A, Pirruccio P, Alberton V, Lococo B, Recalde C, Fazini B, et al.: Histologic versus clinical remission in proliferative lupus nephritis. *Nephrol Dial Transplant* 32: 1338–1344, 2017 PubMed
65. De Rosa M, Azzato F, Toblli JE, De Rosa G, Fuentes F, Nagaraja HN, et al.: A prospective observational cohort study highlights kidney biopsy findings of lupus nephritis patients in remission who flare following withdrawal of maintenance therapy. *Kidney Int* 94: 788–794, 2018 PubMed
66. Turner-Stokes T, Wilson HR, Morreale M, Nunes A, Cairns T, Cook HT, et al.: Positive antineutrophil cytoplasmic antibody serology in patients with lupus nephritis is associated with distinct histopathologic features on renal biopsy. *Kidney Int* 92: 1223–1231, 2017 PubMed
67. Sethi S, Madden BJ, Debiec H, Charlesworth MC, Gross L, Ravindran A, et al.: Exostosin 1/exostosin 2-associated membranous nephropathy. *J Am Soc Nephrol* 30: 1123–1136, 2019 PubMed
68. Mackay M, Dall'Era M, Fishbein J, Kalunian K, Lesser M, Sanchez-Guerrero J, et al.: Establishing surrogate kidney end points for lupus nephritis clinical trials: Development and validation of a novel approach to predict future kidney outcomes. *Arthritis Rheumatol* 71: 411–419, 2019 PubMed
69. Liu Z, Zhang H, Liu Z, Xing C, Fu P, Ni Z, et al.: Multitarget therapy for induction treatment of lupus nephritis: A randomized trial. *Ann Intern Med* 162: 18–26, 2015 PubMed
70. Zhang H, Liu Z, Zhou M, Liu Z, Chen J, Xing C, et al.: Multitarget therapy for maintenance treatment of lupus nephritis. *J Am Soc Nephrol* 28: 3671–3678, 2017 PubMed
71. Rovin BH, Solomons N, Pendergraft WF 3rd, Dooley MA, Tumlin J, Romero-Diaz J, et al.; AURA-LV Study Group: A randomized, controlled double-blind study comparing the efficacy and safety of dose-ranging voclosporin with placebo in achieving remission in patients with active lupus nephritis. *Kidney Int* 95: 219–231, 2019 PubMed
72. Condon MB, Ashby D, Pepper RJ, Cook HT, Levy JB, Griffith M, et al.: Prospective observational single-centre cohort study to evaluate the effectiveness of treating lupus nephritis with rituximab and mycophenolate mofetil but no oral steroids. *Ann Rheum Dis* 72: 1280–1286, 2013 PubMed
73. Rovin BH, Furie R, Latinis K, Looney RJ, Fervenza FC, Sanchez-Guerrero J, et al.; LUNAR Investigator Group: Efficacy and safety of rituximab in patients with active proliferative lupus nephritis: The lupus nephritis assessment with rituximab study. *Arthritis Rheum* 64: 1215–1226, 2012 PubMed
74. Gomez Mendez LM, Cascino MD, Garg J, Katsumoto TR, Brakeman P, Dall'Era M, et al.: Peripheral blood B cell depletion after rituximab and complete response in lupus nephritis. *Clin J Am Soc Nephrol* 13: 1502–1509, 2018 PubMed
75. Chavarot N, Verhelst D, Pardon A, Caudwell V, Mercadal L, Sacchi A, et al.; Groupe Coopératif sur le Lupus Rénal: Rituximab alone as induction therapy for membranous lupus nephritis: A multicenter retrospective study. *Medicine (Baltimore)* 96: e7429, 2017 PubMed
76. Kraaij T, Kamerling SWA, de Rooij ENM, van Daele PLA, Bredewold OW, Bakker JA, et al.: The NET-effect of combining rituximab with belimumab in severe systemic lupus erythematosus. *J Autoimmun* 91: 45–54, 2018 PubMed