Diagnostic and therapeutic advances have changed the paradigm of ANCA associated vasculitis from a fatal diagnosis to a chronic relapsing disease. Avoiding long-term treatment toxicity and preventing, detecting, and treating relapses early are key clinical strategies to reduce organ damage and improve quality of life. Unfortunately, relapses are frequent with traditional oral maintenance immunosuppression, occurring in 50% of patients by 5 years. Recent clinical study design reflects the importance of relapse prevention in current practice, with increased emphasis on sustained remission end points. Optimal management of relapse includes relapse prevention by tailoring therapeutic choices according to predicted relapse risk as well as rapid identification and intervention at the time of relapse to avoid accrual of organ damage with treatments that prevent further relapses.

Increasing therapeutic options for ANCA-associated vasculitis permits the stratification of patients to therapies according to relapse risk, disease severity, and adverse event risk. Relapse risk should be assessed at diagnosis as well as at the end of the remission induction and remission maintenance phases to inform treatment changes. Clinical factors that confer higher relapse risk include proteinase 3–ANCA subtype (versus myeloperoxidase-ANCA), presence of granulomatous disease (versus vasculitic manifestations), ENT disease, lower serum creatinine at presentation, chronic nasal Staphylococcus aureus carriage, and a history of prior relapse (1). Identification of a biomarker to reliably predict impending relapse has proven elusive and remains an important research goal.

Choices of initial remission induction therapy and treatment withdrawal are also major factors in determining relapse risk. Therefore, therapeutic choice should be aligned with clinical predictors of relapse and balanced with disease severity and adverse event risk. Rituximab and cyclophosphamide (each combined with high dose glucocorticoids) are first-line treatments used for severe ANCA-associated vasculitis (2,3) with similar subsequent relapse risk. Mycophenolate is non-inferior to cyclophosphamide for remission induction of severe new disease; however, it is associated with higher subsequent relapse rates (4). Mycophenolate should be reserved for patients with low relapse risk in whom cyclophosphamide and rituximab avoidance are desirable. For non-organ-threatening disease, methotrexate is another alternative to cyclophosphamide, but it is also associated with higher subsequent relapse rates.

For remission maintenance, azathioprine and methotrexate have similar efficacy, with relapse rates of approximately 30% after cyclophosphamide induction over 2 years. Maintenance therapies after rituximab should be considered to prevent relapses, particularly beyond 12–24 months when B cell depletion wanes. Remission maintenance for at least 2 years is currently recommended in all patients (5). Withdrawal of azathioprine and glucocorticoids after a 2-year course is associated with increased relapse risk (6). Factors, such as historical ANCA subtype, ongoing ANCA positivity, and prior relapse history, are important when considering therapy withdrawal. The MAINRITSAN trial (7) demonstrated that rituximab 500 mg every 6 months for 18 months after remission induction with cyclophosphamide is more effective than azathioprine at preventing relapse. For patients at high relapse risk, rituximab for remission maintenance may be required, although it should be balanced against risks of secondary hypogammaglobulinemia and infections. A small proportion of patients with rituximab-induced hypogammaglobulinemia may require long-term immunoglobulin replacement to reduce infections (8). As with withdrawal of other immunosuppression, discontinuation of rituximab after a 2-year maintenance course is associated with significant relapse risk, particularly after B cell reconstitution with rising ANCA levels (9).

Relapses are classified as major (severe) or minor (non-severe) according to the presence or absence of severely damaging or potentially organ-threatening disease. However, untreated minor relapses usually progress to major relapses. Disease activity is often less severe at relapse than at initial diagnosis, reflecting early recognition of relapses and the effect of ongoing background glucocorticoids or immunosuppression. However, for patients without significant prior cyclophosphamide exposure in whom therapies have been withdrawn, relapses can be rapidly progressive, which is of increasing relevance, because rituximab-based induction regimens are reducing cyclophosphamide use. Patient education, access to vasculitis specialists, and appropriate frequency of monitoring visiting are important aspects of patient management.

Treatment of non-severe relapses with a temporary increase in glucocorticoids restores remission in most patients, but recurrent relapses within a short time interval are common. Analysis of 44 patients from the RAVE trial who experienced a minor relapse...
during follow-up found that 80% of patients achieved remission with an increase in prednisone dose; however, 70% had another relapse within 6 months. In patients with frequent relapses, alternative approaches beyond a temporary increase in glucocorticoid should be used. Intensification or modification of the immunosuppressive remission maintenance regimen (e.g., addition or augmentation of azathioprine or methotrexate) is common practice (5). For major relapses, including severely damaging, potentially organ-threatening or life-threatening ANCA-associated vasculitis, rituximab or cyclophosphamide with glucocorticoids is recommended. Notably, rituximab was superior to cyclophosphamide for remission induction for patients with major relapse at the entry to the RAVE trial (2), the majority of whom had previous cyclophosphamide exposure. Consequently, rituximab is being increasingly used to treat major relapse. After relapse, rituximab maintenance therapy may also prove effective for preventing additional relapse; an important question that the soon to be reported RITAZAREM trial (NCT01697267) will help to address.

In this issue of CJASN, Tuin et al. (10) report the results of a randomized, controlled, open label trial of mycophenolate mofetil versus cyclophosphamide for remission induction in patients with relapsing ANCA-associated vasculitis. This trial included patients with severe but non-life-threatening relapses (patients with severe alveolar hemorrhage and creatinine ≥5.66 mg/dl were excluded). Tuin et al. (10) found that, with concomitant high-dose glucocorticoids (60 mg prednisolone per day for 6 weeks tapering to 30 mg at 3 months and 10 mg at 6 months), no statistically significant differences in remission or subsequent relapse rates were observed between the cyclophosphamide and mycophenolate groups. However, in a post hoc analysis, patients with the highest Birmingham Vasculitis Activity Score (BVAS) scores at trial entry were less likely to achieve remission in the mycophenolate group. The observation that mycophenolate might be less effective than cyclophosphamide in patients with the greatest disease activity is potentially very important; however, recruitment was curtailed at 84 patients, limiting the strength of any conclusions that can be drawn. The larger Mycophenolate Mofetil Versus Cyclophosphamide (MYCYC) trial (4) reported noninferiority of mycophenolate compared with cyclophosphamide for remission induction in 140 patients with newly diagnosed severe ANCA-associated vasculitis, where median BVAS was 18 at entry compared with BVAS of 15 at entry in the study by Tuin et al. (10). Glucocorticoid doses were initially high in the MYCYC trial (prednisolone 1 mg/kg daily for the first week), and approximately 50% of patients received intravenous methylprednisolone and/or plasma exchange before trial entry, potentially facilitating initial disease control in the patients with the most active disease.

Tuin et al. (10) found no significant difference in relapse rate between mycophenolate and cyclophosphamide groups using azathioprine maintenance therapy. This is in contrast to the MYCYC trial, where relapses occurred early and were significantly greater in the mycophenolate group. Glucocorticoid taper was more rapid in the MYCYC trial, reducing to 5 mg prednisolone by 6 months. The high relapse rate observed in patients on mycophenolate in the MYCYC trial may reflect a detrimental effect of a temporary reduction in immunosuppression during transition between two short-acting oral immunosuppressants, the effect of a rapid glucocorticoid taper to a low remission maintenance prednisolone dose (5 mg/d), or the absence of prior cyclophosphamide exposure in the patients. The majority of patients in the study by Tuin et al. (10) had received prior cyclophosphamide.

Tuin et al. (10) focused on relapse management, addressing the use of mycophenolate, a therapy with lower long-term cumulative malignancy and infertility risks than cyclophosphamide. The efficacy of alternatives to cyclophosphamide for remission induction is important, particularly in relapsing disease, where previous exposure to cyclophosphamide as initial treatment at diagnosis is common. The result of this study taken in context with the superiority of rituximab to cyclophosphamide for remission induction in relapsing patients in the RAVE trial makes rituximab preferable as first-line treatment for severe relapse. The study by Tuin et al. (10) suggests that mycophenolate with high-dose glucocorticoids is a potential therapy for less active severe or nonsevere disease relapses when additional cyclophosphamide or rituximab avoidance is desirable, although interpretation of results is limited by the small trial size and under-powering.

The important treatment goal in ANCA-associated vasculitis of reducing glucocorticoid toxicity with lower doses and shorter courses was not addressed by Tuin et al. (10). Glucocorticoid-sparing strategies to achieve long-lasting remission are potentially more attractive. Ongoing trials are combining two immunsuppressants with low/no glucocorticoids for this purpose. Examples include the addition of abatacept (CTLA4-Ig) to oral immunosuppression for minor relapse (NCT02108860), the addition of avacopan (C5a receptor antagonist) to rituximab or cyclophosphamide for severe new and relapsing disease (NCT02999427), and the combination of belimumab and rituximab for severe new and relapsing disease (EUDRACT number 2017–004645–24).

Improvements in early outcomes have made the prevention, identification, and treatment of relapses in ANCA-associated vasculitis important. Rituximab and cyclophosphamide remain first-line treatment for severe relapse, with rituximab favored over cyclophosphamide in patients with significant prior cyclophosphamide exposure. Mycophenolate with high-dose glucocorticoids may be considered for severe, nonlife-threatening relapse when cyclophosphamide and rituximab avoidance is desirable, although it should be used with caution in patients with highly active disease. Novel glucocorticoid-sparing approaches for relapse management are potentially more appealing than regimens requiring high-dose glucocorticoids.

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