Title
Rituximab for maintenance of remission in ANCA associated vasculitis: expert consensus guidelines

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Background

Anti-neutrophil cytoplasm antibody (ANCA) associated vasculitis (AAV) encompasses three disease phenotypes: granulomatosis with polyangiitis (GPA), microscopic polyangiitis (MPA) and eosinophilic granulomatosis with polyangiitis (EGPA). Considerable improvements in therapy mean induction of remission occurs in most patients with AAV (1-4). However, disease relapse continues to pose a burden to patients. Morbidity accrues with relapses through disease related damage and adverse effects of therapies to manage these relapses, negatively impacting on quality of life (5).

Rituximab (RTX), a monoclonal antibody targeting CD20, leads to peripheral B cell depletion. This has been successfully trialled, and is licensed, for the induction and maintenance of remission in AAV (2, 3). RTX is increasingly being used for the maintenance of remission in patients with AAV, to reduce the risk of relapse and its consequences (6).

We present guidelines developed through a modified Delphi exercise on the use of rituximab in the maintenance of remission in adult AAV patients, with additional focus on adjunct therapies, adverse effects and use of prophylaxis.

Methods

This modified Delphi exercise invited experts in the management of AAV practising in the United Kingdom to participate. The group of clinicians included 11 nephrologists, 8 rheumatologists and 1 paediatric rheumatologist.

The modified Delphi exercise was planned with four rounds, including a face-to-face meeting. The first round sought to identify key areas for the scope of these guidelines and systematic literature review. The literature search was conducted using key search strings of systemic vasculitis, granulomatosis with polyangiitis, microscopic polyangiitis and eosinophilic granulomatosis with polyangiitis, including eponymous names where applicable, combined with rituximab, CD20 and/or B lymphocytes as appropriate for each database (full search string in supplementary material). Studies including at least 20 patients receiving at least two infusions of rituximab were included. The literature review addressing the key issues identified from the first round was presented to each participant with a summary of responses.

Following a third round, an expanded literature review was produced to address important issues with limited evidence in AAV. An expanded literature search of studies on pneumocystis jirovecii pneumonia prophylaxis, vaccination, late onset neutropenia and hypogammaglobulinaemia in autoimmune disease was conducted (full search strategy provided in supplementary material).

A final vote determined the level of agreement; a level of 80% was prespecified for inclusion in these guidelines. No statement was excluded for this reason. Prior to the final voting round, the guidelines were distributed to clinicians not involved in guideline development and patient participants in order to assess their face validity and clinical utility.

The Oxford Centre for Evidence-Based Medicine 2011 Levels of Evidence were used to grade the level of evidence for each statement (7).
The Birmingham Vasculitis Activity Score (BVAS) or GPA specific measure BVAS/WG are used for assessment of disease activity (8, 9). In these guidelines, the disease states used are: active disease, disease remission, refractory disease, and relapse.

Active disease: manifestations attributable to AAV, and not due to disease related damage

Disease remission: disease control (BVAS or BVAS/WG ≤1); glucocorticoid free remission refers to disease control (BVAS or BVAS/WG ≤ 1) off glucocorticoid therapy.

Refractory disease: despite treatment of disease, remission has not been established, with persistent or progressive disease activity.

Disease relapse: where disease activity has previously been controlled, and has become active, defined by at least 1 unit increase in BVAS.

- Major relapse: relapse with 1 new, recurrent or worsening major item on BVAS or BVAS/WG
- Minor relapse: relapse without a major item on BVAS or BVAS/WG
Statements

1. When should rituximab be used for the maintenance of remission in AAV?
   
a. GPA/MPA – new and relapsing patients

We recommend the use of rituximab for the maintenance of remission in patients with GPA and MPA following rituximab induction. Rituximab maintenance can also be considered after cyclophosphamide induction.

Level of evidence: 1b (following cyclophosphamide induction) 2b (following rituximab induction)

Grade of recommendation: A (after cyclophosphamide induction) B (after rituximab induction)

Vote: 18/18 (100%)

Two randomised controlled trials (RCT) have evaluated the efficacy of RTX for the maintenance of remission in AAV (10, 11). The MAINRITSAN trial randomised 115 patients with newly diagnosed (80%) or relapsing (20%) AAV (excluding EGPA) to receive a RTX or azathioprine based maintenance regimen following remission induction with cyclophosphamide (10). The RTX regimen was two 500 mg doses of RTX a fortnight apart after remission induction followed by 500 mg every six months until month 18 (i.e. 3 further doses). After 28 months, fewer major relapses occurred in patients who received RTX compared with azathioprine (5% vs 29%, hazard ratio 6.61, 95% confidence interval (CI) 1.56 to 27.96, p = 0.002), resulting in a number needed to treat of 4 patients to prevent one major relapse (10). The superiority of rituximab over azathioprine in relapse prevention persisted at 60 months’ follow-up (12).

MAINRITSAN2, compared the fixed-schedule RTX dosing from the MAINRITSAN trial with an individually tailored RTX maintenance regimen, where after an initial maintenance infusion of 500 mg RTX x2, further 500 mg doses were administered based on 3-monthly measures of ANCA and B cells (11). In this trial, RTX induction was used in 37% of patients. At 28 months after the first maintenance RTX infusion, 8 (9.9%) patients receiving fixed-schedule RTX had relapsed (3 major) compared with 13 (16.0%) patients experiencing 14 relapses (6 major) in the tailored infusion arm.

One ongoing RCT, RITAZAREM (NCT01697267), compares 4 monthly 1000mg RTX dosing with azathioprine for the maintenance of remission following RTX induction in patients with a relapse of AAV (13).

Several observational studies, with follow-up to 7.6 years, provide further evidence on the safety and efficacy of RTX for the maintenance of remission in patients with new, relapsing and refractory AAV (14-21). Reflecting current practice patterns, these studies have largely used RTX to maintain remission after successful RTX induction.

a. EGPA patients

Despite limited evidence regarding the use of rituximab for the maintenance of remission in EGPA, we advise a similar approach to GPA and MPA. Overall responses to rituximab may differ to GPA and MPA, and steroid withdrawal may be more challenging.
EGPA is a relatively understudied subgroup of AAV, owing to phenotypic differences to GPA and MPA, and relative rarity of disease. Published trials of RTX for induction and maintenance of remission in AAV have not included patients with EGPA. One multi-centre retrospective case series of 41 patients with predominantly refractory or relapsing EGPA reported a clinical improvement in 83% by 6 months, with 34% achieving complete remission (22). Prednisolone cessation was possible in only 2 patients at 12 months. In a single centre including 69 patients with EGPA, similar remission rates were identified (34% at 6 months and 49% at 12 months) (23). Median prednisolone doses were 7.25 mg/day at 12 months and 5 mg/day at 24 months. Relapse was common, with 54% of patients relapsing, predominantly due to uncontrolled asthma or other respiratory manifestations. In both studies, patients who were ANCA positive were more likely to achieve remission.

An ongoing RCT, MAINRITSEG (NCT02807103), is evaluating RTX in patients with EGPA for maintenance of remission (24).

2. What rituximab maintenance regimen should be used for AAV?

   a. Dose and dosing intervals

   We recommend fixed interval dosing with rituximab either 500 mg or 1000 mg administered every 6 months for a period of 2 years. There is ongoing relapse risk after rituximab withdrawal and patients should be monitored accordingly.

   Level of evidence: 1b
   Grade of recommendation: B
   Vote: 18/18 (100%)

This regimen is recommended following the completion of induction therapy. The treatment regimen should be individualised, particularly in post-pubertal adolescents and older individuals with comorbidities where concerns regarding adverse effects exist. There is limited data for the use of RTX in children.

No direct comparisons have been made between the two most commonly used doses of RTX- 500 mg and 1000 mg. Both published RCTs have used 500 mg doses of RTX whilst observational studies have largely used 1000 mg doses and this dose is being used in the ongoing RITAZAREM trial (10, 11, 14, 16-18). Whilst observational cohorts include a greater proportion of patients with relapsing or refractory disease than RCTs, it is unknown if the dose of RTX influences clinical outcomes in these patients.

There are two main approaches to RTX dosing intervals; fixed interval dosing and biomarker guided dosing. As detailed above, the MAINRITSAN2 trial compared fixed 6 monthly RTX infusions with
dosing based on 3 monthly assessments for ANCA return or increase and B cell return (11). At 28 months’ follow-up, no difference in relapse rate was identified between the two groups (p=0.22); 8/81 (9.9%) of patients receiving fixed interval dosing had experienced 8 relapses including 3 major relapses, whereas 13/81 (16.0%) patients with repeat dosing determined by biomarker changes had experienced 14 relapses including 6 major. No difference in serious adverse events related to infection was identified, with 16 individuals receiving fixed interval RTX having 18 infections and 9 individuals with tailored dosing having 18 infections.

The role of biomarker guided RTX dosing has not been proven and requires further study, including the evaluation of long-term outcomes. Relapses in spite of ANCA negativity and B cell depletion have been observed in both RCTs and observational studies (10-12, 16-18, 21, 25). Fixed interval dosing has therefore been recommended. As discussed below, in selected patients, biomarker fluctuations, comorbidities and adverse effects may necessitate a more individualised approach to RTX dose and dosing intervals.

b. Management of relapse despite maintenance rituximab

Changes to treatment in refractory disease or relapse despite induction and rituximab maintenance therapy should be determined according to severity of disease activity and organ involvement.

A guide to treatment decisions is presented.

Level of evidence: 4  
Grade of recommendation: C  
Vote: 18/18 (100%)

In view of the rarity of refractory disease or relapse on RTX maintenance therapy, there are no studies specifically evaluating treatment approaches. Various strategies have been adopted in specialised centres and described in RCTs and observational studies (10, 11, 14, 16, 17).

Referral to a specialist centre is advised. Assessment requires careful consideration of the relative contribution of disease damage and activity to patient symptoms, alternative diagnoses, and potential disease drivers including infection, nasal carriage of Staphylococcus aureus, and cocaine use.

Treatment of disease activity should depend on its severity, including consideration of major organ involvement and whether any benefit from RTX has been derived. For example, major organ involvement typically necessitates re-induction therapy. Shortened interval dosing is considered where disease activity emerges shortly prior to scheduled infusions, and the addition of concomitant immunosuppression could be considered where, despite a response to RTX, there is mild persistent disease activity without major organ manifestations. Concomitant therapy includes traditional maintenance agents (e.g. azathioprine, methotrexate or mycophenolate), or low dose glucocorticoids (≤ 5 mg/d prednisolone, or equivalent). In the event of RTX failure, alternative maintenance strategies should be considered.
c. Extended rituximab maintenance therapy

In selected patients, relapse risk remains high after 2 years of maintenance therapy, and extended duration therapy could be considered. This includes patients who relapse after a prior course of rituximab maintenance, with persistent elevation or return of ANCA, or where the consequence of relapse would be organ or life threatening.

Optimal treatment approaches beyond 2 years are yet to be determined. 500 mg – 1000 mg every 6 to 12 months for up to 5 years could be considered. In patients with prior relapse after maintenance rituximab cessation, this could be adjusted based on time from treatment cessation to disease relapse.

Level of evidence: 5
Grade of recommendation: D
Vote: 17/18 (94.4%)

Long-term follow-up data from the MAINRITSAN trial highlights the risk of relapse after RTX cessation (12). Until 28 months’ follow-up, 10 months after the last RTX infusion, only 3 (5%) patients experienced a major relapse. Over the subsequent 22 months, without further scheduled RTX infusions, an additional 13 (23%) patients experienced a major relapse. Consistent with this, rituximab maintenance cohorts demonstrate a progressive reduction in relapse-free survival after rituximab cessation (17, 18). An ongoing RCT (MAINRITSAN3) compares the effects of extended RTX maintenance with standard duration therapy (NCT02433522) (26).

Optimal regimens for extended RTX maintenance require further study. Extended treatment to 5 years is proposed in patients at high risk of relapse or its consequences. The dosing strategy presented (figure 1) is a guide, derived by expert consensus. Individualisation of any extended treatment regimen is emphasised, based on the patient’s wishes, comorbidities, age, and the history of their AAV.

Identifying patients at greatest risk of relapse after RTX treatment remains challenging. Patients who have relapsed after a previous course of RTX are considered empirically to be at greater risk of further relapse.

Patients who are ANCA positive either through persistent positivity or return, are likely to have a greater risk of relapse. Notably, in the MAINRITSAN trial, the risk of relapse for patients who were ANCA positive at each follow-up visit increased over time (12). Following RTX cessation, one cohort reported that switching from negative to positive ANCA status was predictive of subsequent relapse (17). This is consistent with findings from the REMAIN trial, which randomised patients who had completed 18-24 months of treatment to continue or withdraw maintenance azathioprine and glucocorticoid (27). The withdrawal of azathioprine maintenance therapy and ANCA positivity at randomisation (i.e. 18-24 months after commencement of treatment) increased the risk of relapse.

Traditional risk factors for relapse such as PR3-associated disease, GPA phenotype and the absence of renal involvement should also be considered in assessing the overall risk of relapse (10, 28, 29).

The risk of relapse must be balanced against potential adverse effects of ongoing RTX. Observational cohorts of patients with AAV have not identified a clear association between cumulative rituximab
d. Role of biomarkers in rituximab maintenance therapy

Further research is needed to consider the role of biomarkers (e.g. ANCA and B cell return) in guiding rituximab maintenance therapy in AAV.

Level of evidence: 2a
Grade of recommendation: B
Vote: 18/18 (100%)

The routine use of biomarkers, such as B cell counts and ANCA, in guiding therapy in AAV is historically contentious (32). As discussed above, relapses continue to occur in the absence of such biomarkers (11, 12, 17). Moreover, treatment regimens thus far have not incorporated measures of treatment related to toxicity including infection rates and immunoglobulin levels, in guiding further therapy.

Whilst these biomarkers should not determine treatment decisions in isolation, the results of long-term studies and the MAINRITSAN2 trial suggests that the use of ANCA and B cell return can be considered in guiding treatment decisions in association with other patient and disease related factors (11, 12, 17).

The validation of alternative biomarkers for disease activity, disease related damage and adverse effects of therapy is required.

3. Concomitant therapy

a. Concomitant immunosuppressive agents/disease modifying anti-rheumatic drugs

Where rituximab is commenced in a patient already receiving a DMARD for remission maintenance (e.g. azathioprine, methotrexate or mycophenolate), we suggest that the existing DMARD(s) be withdrawn.

Level of evidence: 4
Grade of recommendation: C
Vote: 15/18 (83.3%)

Concomitant therapy refers to concurrent use of another non-glucocorticoid immunosuppressive or disease modifying anti-rheumatic drug with RTX.

In clinical trials of RTX for the maintenance of remission in AAV, concomitant therapy has not been used. In observational cohorts, where patients are already receiving a non-glucocorticoid immunosuppressive agent as maintenance therapy and RTX has been added, there has usually been
withdrawal of this medication (14-17). Owing to the potential for increased adverse effects, the routine use of concomitant therapy has therefore not been recommended.

There is limited evidence from small numbers of patients receiving RTX maintenance treatment with refractory or relapsing disease described in observational studies, suggesting concomitant therapy may be efficacious in this setting (14, 17). Rare cases of persistent disease activity despite ongoing RTX maintenance therapy may benefit from the addition of a concomitant immunosuppressive agent.

a. **Glucocorticoids**

Glucocorticoid tapering strategies should aim for complete cessation 6-12 months after rituximab commencement.

Level of evidence: 5

Strength of recommendation: D

Vote: 17/18 (94.4%)

Glucocorticoid-free remission remains ideal in view of known, predictable adverse effects. In long term follow-up of patients enrolled in European RCTs, prolonged glucocorticoid use was associated with greater disease damage, after adjusting for number of relapses during follow-up, age, baseline disease activity and renal involvement (33).

Shorter glucocorticoid tapering strategies are possible in many patients with AAV. One RCT that randomised patients to RTX induction or cyclophosphamide followed by azathioprine maintenance, provided a standardised glucocorticoid taper to cessation at 6 months to patients in both arms (34). Glucocorticoid free remission was achieved in 64% of the RTX treated patients and 53% of those who received cyclophosphamide. Completed RCTs of rituximab for the maintenance of remission have used glucocorticoid protocols allowing for glucocorticoid reduction in the first 6-12 months, but typically continue at low dose until at least 18 months following induction therapy (10, 11). In uncontrolled settings, earlier prednisolone dose reduction and cessation is well documented with RTX maintenance therapy (15-17).

In practice, patients with EGPA have greater difficulty with glucocorticoid withdrawal, often resulting in incomplete control of asthma symptoms (22). Adrenal insufficiency may also prohibit complicate the cessation of glucocorticoids (35, 36).

4. **Prophylaxis**

   a. **Pneumocystis jirovecii prophylaxis**

   *Pneumocystis jirovecii* (PJP) prophylaxis is suggested in all patients receiving rituximab maintenance therapy.

   Level of evidence: 4
Grade of recommendation: C

Vote: 16/18 (88.9%)

PJP prophylaxis is encouraged for at least 6 months from commencement of induction therapy for AAV. In RCTs of RTX maintenance, 2 cases of PJP were identified in patients on RTX, neither of whom were on prophylactic therapy at the time of PJP diagnosis (12).

There is a paucity of information comparing PJP prophylaxis strategies in patients immunosuppressed for autoimmune disease including ANCA associated vasculitis. In trials of RTX in AAV, PJP prophylaxis strategies have varied, most commonly using combination trimethoprim and sulfamethoxazole (2, 3, 10, 11). Data for the use of alternative agents, including pentamidine inhalation, dapsone and atovoquone are limited owing to the rarity of use.

Extended duration of prophylaxis is recommended in patients considered to be at high risk. The following factors influence the incidence of PJP: lymphopenia (especially low CD4+ T cell counts), increased age, prolonged use of glucocorticoid or other immunosuppression, and structural lung disease including chronic obstructive pulmonary disease (COPD).

Similar to solid organ transplant, local clusters of patients with PJP have been identified in patients immunosuppressed for autoimmune disease, including AAV (37). Recomencement of prophylaxis in individuals with ongoing immunosuppression should be considered when a local cluster of PJP is identified.

b. Vaccination

Influenza and pneumococcal vaccinations should be recommended to all patients. Live vaccinations should be avoided.

Although vaccinations are ideally provided at least 1 month prior to rituximab infusion, timing should not preclude vaccination.

Level of evidence: 5

Grade of recommendation: D

Vote: 18/18 (100%)

Infections remain a significant source of morbidity and mortality in patients with AAV, with a predominance of respiratory tract infections (11, 12, 38, 39).

The protective benefit of influenza vaccination in the general population is well established. Despite previous reports on vaccinations precipitating disease activity in patients with AAV, a small RCT and observational cohort support the safety of influenza vaccination in patients with AAV (40, 41).

In patients receiving RTX maintenance therapy, inefficacy remains a concern, particularly where B cell depletion persists. The efficacy of vaccination in patients receiving RTX maintenance has not been evaluated AAV. Albeit blunted and in a smaller proportion compared with those receiving methotrexate, vaccination response has been demonstrated in patients with rheumatoid arthritis 6
months post-RTX despite incomplete B cell repopulation in most patients (42). Vaccination at least one month prior to RTX is recommended to maximise vaccination effect. However, given the practical implications of treatment timelines and seasonal nature of infections, vaccinations outside of the ideal timeframe in spite of potential inefficacy often remains appropriate.

5 a. Hypogammaglobulinaemia

i) In the setting of rituximab maintenance therapy:
   a) Immunoglobulins should be monitored in all patients
   b) Further investigation is recommended for:
      ▪ Recurrent or atypical infections; OR
      ▪ IgG <3 (in paediatric age ranges, IgG less than the age appropriate lower limit of normal should be used).

   Level of evidence: 2a [part a], 5 [part B]
   Grade of recommendation: B [part a] D [part b]
   Vote: 18/18 (100%)

Despite stable IgG levels reported by RCTs of RTX maintenance therapy, hypogammaglobulinaemia has been consistently observed in observational cohorts of patients receiving RTX (10, 11, 30, 31). Conflicting results are likely a result of multiple factors; observational cohorts include a greater proportion of patients with a higher burden of prior immunosuppression for refractory or relapsing disease, hypogammaglobulinaemia is variably defined, is transient in some and can be a late complication. Whilst long term data is limited, the primary concern with persistent hypogammaglobulinaemia is recurrent, chronic and/or atypical infections.

It is not known whether rituximab should be withheld for low or falling IgG levels and in clinical trials a threshold of 3g/L has been used (13). The possibility that continued rituximab will exacerbate hypogammaglobulinemia should be considered.

Patients with an established pattern of recurrent or atypical infections and hypogammaglobulinaemia may benefit from interventions including prophylactic antimicrobial therapy and/or immunoglobulin replacement. This should be considered in these subgroups of patients in accordance with local guidelines.

Consistent with other recently published guidelines, whilst patients with persistent IgG < 3 g/L without infections may not require further intervention, their infection profile and vaccination responses should be reviewed, in conjunction with Clinical Immunology services (43, 44). For patients in paediatric age ranges, the long-term implications of hypogammaglobulinaemia are of greater concern and Clinical Immunology review should be sought when IgG levels fall below age adjusted norms.

ii) Parallel administration of rituximab and immunoglobulin replacement could be considered in patients with hypogammaglobulinaemia and a clinically important response to rituximab is anticipated.
In rare circumstances, relapse of AAV occurs in patients receiving immunoglobulin replacement therapy for hypogammaglobulinaemia. Uncontrolled disease typically necessitates further immunosuppression despite an established immunodeficient state. The additive effect of RTX associated hypogammaglobulinaemia with other immunosuppressive agents, thereby targeting multiple immune pathways, is unclear.

Decisions on co-administration of RTX and immunoglobulin replacement, and the timing of these agents should be in conjunction with Clinical Immunology.

5 b. late onset neutropenia

Clinicians and patients should be aware of the possibility of late onset neutropenia with rituximab use. A history of uncomplicated late onset neutropenia does not prohibit future rituximab use.

Level of evidence: 4
Grade of recommendation: C
Vote: 16/18 (88.9%)

In patients with a history of late onset neutropenia, there should be greater clinician and patient vigilance of infective symptoms after future RTX administration.

Late onset neutropenia is incompletely understood but postulated to result from arrest of granulopoiesis in favour of B cell lymphopoiesis (45). Late onset neutropenia has been identified in patients in RTX maintenance cohorts and RCTs (11, 14, 17, 18, 46, 47). Owing to the unpredictable timing of late onset neutropenia, regular evaluation for neutropenia is not routine. The neutropenia is often asymptomatic, typically short-lived and, in the absence of routine testing, therefore likely under-recognised. Late onset neutropenia often recovers without therapy, with granulocyte colony stimulating factor (G-CSF) used in symptomatic patients with prolonged neutropenia, or with infective symptoms in conjunction with anti-microbial therapy. Moreover, reports of recurrence in patients treated for autoimmune disease, including AAV, are uncommon (48, 49). In patients with a history of neutropenia complicated by severe infection, there is limited experience in repeat RTX administration.

Research agenda

In addition to the areas discussed already, the following issues were identified as areas requiring further research and evidence.

1. Impact of maintenance therapy on health-related quality of life.
2. The effects of extended rituximab maintenance therapy.
   a. Adverse effects of treatment including neutropenia, progressive multifocal leukoencephalopathy and long term outcomes of hypogammaglobulinaemia.
   b. Longer term outcome of patients with rituximab maintenance therapy including disease related damage and cardiovascular risk.
   c. Health economics analysis of rituximab maintenance therapy and extended rituximab maintenance therapy.

3. Prediction of relapse including the role of biomarkers (e.g. ANCA, CD19, CD27, serum calprotectin) for risk of relapse.

4. Impact of rituximab for the maintenance of remission in special populations and situations:
   a. paediatric patients;
   b. fertility; and
   c. pregnancy.

Conclusion

Induction treatment for AAV is increasingly successful at achieving remission, and optimal maintenance of remission has become a key priority in the long-term management of these patients. The clinical efficacy of RTX in both the induction and maintenance of remission has been demonstrated in clinical trials (2, 3, 10-12). Developed through a modified Delphi exercise involving an expert group, we present guidelines that consider both the RCT and wealth of non-trial experience in the use of RTX for the maintenance of remission in AAV.

References

Completion of induction therapy & rituximab selected for maintenance of remission

Complete response

2 years

6 monthly rituximab
Aim for complete glucocorticoid withdrawal

Maintenance of remission

Disease relapse

Refractory disease

Refractory or relapsing disease

Consider:
- whether symptoms relate to disease activity or disease damage
- alternative diagnosis or concomitant diagnosis
- additional disease drivers (e.g., infection, cocaine use)
- incomplete B cell depletion

Possible management options:
- repeat induction therapy (change induction agent(s) or repeat rituximab induction can be considered)
- shorten interval between rituximab infusions
- concomitant therapy (e.g., azathioprine, mycophenolate, methotrexate)
- consider research studies

High risk

Standard risk

Consider extended rituximab maintenance therapy if:
1. Prior relapse following cessation of rituximab maintenance
2. ANCA persistence or return
3. Further relapse anticipated to be organ or life threatening

Maintenance of remission

Cease rituximab and monitor for relapse

Disease relapse