Maintenance therapy for ANCA-associated vasculitis

Scope

This guideline applies to the management of patients with ANCA-associated vasculitis (AAV) and specifically to the management strategy for maintenance of disease remission. Treatment should be led and supervised by a consultant (renal, rheumatology or respiratory) with experience and expertise in the management of this group of patients.

Rationale

The purpose of this guideline is to provide evidence-based, uniform guidance for maintenance of remission in ANCA-associated vasculitis.

Background

Once full remission of ANCA –associated vasculitis (AAV) has been induced, the main goal is the prevention of relapses. Relapses cause damage and morbidity, and are an important determinant of ESRD(1). Although the prognosis of AAV has improved, the risk of relapse remains high, occurring in 38% at 5 years in a meta-analysis of the first wave EUVAS trials(2), and in 32% at 18 months after a single course of rituximab-based induction therapy without maintenance(3), demanding vigilance with life-long clinical follow-up.

For the prevention of relapses, azathioprine, methotrexate, rituximab or MMF, often with low-dose glucocorticoids, are used and recommended for at least 24 months following induction of remission(4).

Which drug treatment for maintenance therapy?

The MAINRITSAN (Efficacy Study of Two Treatments in the Remission of Vasculitis) trial compared low-dose rituximab in GPA/MPA (at a fixed 500 mg dose) to tapering dose of azathioprine for remission maintenance after induction with pulsed cyclophosphamide. At month 28, major relapses had occurred: 17 in the azathioprine group and 3 in the rituximab group. Renal relapses occurred in 8/17 major relapses in the azathioprine group and 0/3 in the rituximab group. The superiority of rituximab maintenance therapy over azathioprine has also been shown in a second clinical trial RITAZAREM, which compared rituximab 1g 4 monthly for 5 doses (all fixed) following a major relapse treated with rituximab induction therapy compared with azathioprine maintenance therapy. 170 patients were randomised. By 24 moths 11/85 patients treated with rituximab and 32/85 patients in the azathioprine group experienced a relapse. Hypogammaglobulinaemia was more common in the rituximab group but there was no difference in other adverse events (5).

Rituximab can be dosed on a regular basis or individually tailored using biomarkers of B cell repopulation and/or rise of ANCA titre to guide re-treatment(6). 162 patients were randomised to receive 3 fixed doses of 500mg rituximab 6 monthly or 500mg rituximab infusion at 6 months and only retreated if when CD19+B lymphocytes or ANCA had reappeared or ANCA titre rose markedly based on trimestrial testing until month 18. All patients received 2g rituximab induction of remission therapy. At month 28, 21 patients had suffered 22 relapses: 14/81 (17.3%) in 13 tailored-infusion

recipients and 8/81 (9.9%) in 8 fixed-schedule patients (p=0.22). The tailored-infusion versus fixed-schedule group, respectively, received 248 vs 381 infusions, with medians (IQR) of 3 (2-4) vs 5 (5-5) administrations.

Azathioprine is preferred over mycophenolate mofetil for remission maintenance, because of the results from the IMPROVE (Mycophenolate Mofetil Versus Azathioprine for Maintenance Therapy in ANCA Associated Systemic Vasculitis) trial. In both groups the remission maintenance agent was reduced at two time points (after 12 months and 18 months) and withdrawn after 42 months. Relapses were noted in 42 participants treated with mycophenolate mofetil and in 30 participants in the azathioprine group (p<0.01). There does not appear to be any difference between azathioprine and methotrexate in maintaining remission or adverse events. However methotrexate should not be used in those with kidney disease due to increased side-effects.

No differences were noted in relapse rates or safety in a trial of azathioprine compared with methotrexate for maintenance of remission either at end of the trial or on long-term follow up(7, 8). Those patients with impaired renal function should not be treated with methotrexate.

The addition of trimethoprim/sulfamethoxazole (800/160 mg twice daily) to standard remission maintenance can reduce the risk of relapse in GPA. Although trimethoprim/sulfamethoxazole has been used as the sole remission maintenance agent in half the patients of one RCT, trimethoprim/sulfamethoxazole monotherapy may not be effective for maintenance of remission. In patients with nasal disease, treatment with topical antibiotics such as mupirocin may be considered in the presence of chronic carriage of nasal *Staphylococcus aureus.*

Duration of maintenance therapy

A Cochrane review of AAV management found one report on immunosuppression duration (9). An updated literature search to July 2020, identified 2 additional studies (10, 11). Studies were selected if they included patients with AAV, compared shorter and longer durations of immunosuppression, used a clinical efficacy outcome and had a RCT design. The three randomised trials identified compared 2 years versus 4 years immunosuppression for AAV relapse prevention. One showed no benefit of longer therapy (45 participants), but poor recruitment limited statistical power (11).The Karras trial (117 participants) and MAINRITSAN 3 trial (97 participants) demonstrated benefit of long-term immunosuppression (10, 12). In the Karras trial, immunosuppression for 2-years was associated with higher relapse rates compared with 4-years treatment duration (63% vs 22%, p<0.0001, Odds Ratio 5.96, 95% Confidence Interval (CI) 2.58 to 13.77)(12). MAINRITSAN 3 investigated the immunosuppressant, rituximab, for 2 years compared to placebo following 2 years of rituximab therapy in AAV. The rituximab group had better relapse free survival (96%; 95% CI 91%-100%) compared to placebo (74%; 95% CI 63%-88%) with a hazard ratio of 7.5 (95% CI, 1.67 to 33.7) (*P* = 0.008). Despite showing differences in the risk of relapse, neither study demonstrated differences in adverse events, infection or disease related damage. The proportion of patients receiving long-term immunosuppression in this study who were over-treated is high.

A retrospective post hoc analysis of long term data in patients recruited to 6 clinical trials of induction maintenance therapy(13) suggested no difference in relapse rates using immunosuppression >18 months compared with <18 months (p=0.11; 308 participants). However, in

all trials, immunosuppression was not protocolised beyond study end and 50% of patients were excluded from analysis (13).

Duration of corticosteroid therapy

Long-term glucocorticoids require a carful risk-benefit assessment, particularly in terms of co-morbidities such as diabetes, cardiovascular disease and infections. The duration of glucocorticoid use has been associated with total damage in AAV (4). In AAV, damage may reflect the higher steroid doses given for more severe disease, but it also represents accumulated irreversible damage due to disease-related factors (14).

So far, there is no randomized control trial that specifically addressed long-term low-dose glucocorticoids for the prevention of relapses. In a meta-analysis before rituximab was used, a longer course of glucocorticoid intake beyond 12 months was associated with fewer relapses(15). A single-centre analysis reported no increase of relapse when glucocorticoids were withdrawn after 6 months, but infection rate was higher in patients receiving glucocorticoids beyond 6 months. Importantly, no increase in adverse events was observed at a dose of 5 mg daily (16).

Biomarkers

The role of ANCA testing as a means of predicting future relapse is controversial and evolving. A negative ANCA does not rule out AAV activity in the appropriate clinical context of active disease. Some studies have shown that patients in whom the ANCA titres either persist, rise fourfold or become positive have a higher incidence of relapse, while other studies do not confirm this association. In these situations, careful observation is highly indicated, but importantly, initiation of treatment is generally not based on ANCA levels.

Also, clinical factors have been related to a higher risk of relapse, such as the diagnosis of GPA, upper respiratory tract vasculitis, pulmonary and cardiovascular involvement as well as chronic nasal *Staphylococcus aureus* carriage

Dialysis patients

Patients on dialysis have a reduced risk of disease relapse but an increased risk of infection. Consideration should be given to early withdrawal of maintenance therapy in these patients to reduce the infectious burden.

Guideline

Maintenance therapy following cyclophosphamide induction

a. Patients who receive induction therapy with cyclophosphamide should be commenced on azathioprine (1mg/kg) 3-4 weeks after the last pulse of cyclophosphamide. If tolerated dose should be increased to 2mg/kg after 4 weeks. TPMT testing is not mandatory.

OR

Commenced on Methotrexate if eGFR>60ml/min. The dose should be started at 10mg/weekly and increased at 4 weekly intervals until therapeutic dose of 20-25mg/week is achieved. Patients should be prescribed folic acid 5mg weekly to reduce side-effects.

b. Low dose steroids (5mg od) plus azathioprine or methotrexate if eGFR>60ml/min should be continued for a minimum of 24 months following remission.

c. Patients who do not tolerate azathioprine or methotrexate should be switched to mycophenolate mofetil. The dose should be started at 500mg bd and increased at 2 weekly intervals until therapeutic dose of 1g bd.

d. Only patients with nasal disease and staph aureus carriage should be considered to continue oral septrin following discontinuation of cyclophosphamide and not routinely used during maintenance therapy.

e. Monitor full blood count weekly for all immunosuppressants for first 4 weeks following stable dose of immunosuppressant thereafter reduce frequency of monitoring to at least every 3 months.

f. Maintenance therapy should be continued for 2-4 years unless there is significant toxicity associated with immunosuppression

Maintenance therapy following rituximab induction at initial presentation

a. Patients who receive induction therapy with rituximab should be commenced on maintenance therapy as above for cyclophosphamide, 4 months after rituximab infusion. If intolerant of azathioprine, methotrexate or mycophenolate rituximab maintenance should be considered.

b. Only patients with nasal disease and staph aureus carriage should consider continuing oral septrin following 6 months of prophylaxis. Routine usage is not necessary

c. Monitor full blood count weekly for first 4 weeks after starting cytotoxic thereafter reduce frequency of monitoring to at least every 3 months as per local policy.

Maintenance therapy following rituximab induction for relapsing disease

a. Patients who have relapsed while on maintenance therapy with a standard maintenance agent and achieved remission following rituximab re-induction therapy should be commenced on rituximab 500mg 6 monthly plus low dose steroids (5mg) for 2 years.

b. If the patient has had more than 1 relapse or relapsed after discontinuing rituximab, maintenance rituximab should be continued for 4 years. The optimal duration of rituximab therapy is unknown.

c. Methylprednisolone 100mg, piriton 10mg IV and paracetamol 1g oral should be co-administered with rituximab as per local policy

d. Hepatitis B serology, specifically HBc Ab and HBs Antigen should be checked before each infusion

e. Low dose steroids (5mg od) plus rituximab should be continued for at least 12 months following remission, consideration should be given to withdrawal after this time.
f. Co-trimoxazole prophylaxis should be continued for maintenance rituximab therapy to reduce risk of all cause infections(17).
g. Stop other immunosuppressants while on rituximab maintenance therapy

Duration of Maintenance steroid therapy and withdrawal

a. If patients have had no disease relapse within 24 months of remission consideration should be given to steroid withdrawal.
b. A 9am cortisol test should be performed prior to steroid withdrawal if cortisol <350nmol/l, patients should be transferred to hydrocortisone (10mg am and 5mg lunchtime) and a short synacthen test (SST) should be performed. If SST failed (30 minute cortisol <450 nmol/l) hydrocortisone should not be. If cortisol >350nmol/l or SST passed corticosteroid should be stopped.
c. The patient should continue on other immunosuppressive therapy for a further 6-12 months before consideration of stopping if no relapses in the interim period.

ANCA monitoring

a. ANCA should not be routinely tested more frequently than every 3 months
b. A change in ANCA level or negative to positive should not be used alone as a basis to change therapy but be used in combination with a structured clinical assessment to inform decisions on changes in treatment for AAV.

Additional advice

a. all patients on maintenance immunosuppressive therapy should be advised about reducing sun exposure and use of sun block to decrease the risk of cutaneous cancers
b. For patients of child-bearing age adequate contraception must be used if receive rituximab, mycophenolate or methotrexate
c. Immunoglobulin levels should be checked annually. If hypogammaglobulinaemic consideration should be given to discontinuation of maintenance immunosuppressive therapy or dose reduction
d. Live vaccines should not be administered. Pneumococcus vaccination should be repeated every 5 years. Annual flu vaccination should be given to all patients. If possible vaccination should be given 4 weeks prior to rituximab administration if receiving maintenance therapy.
e. Annual review of cardiovascular risk should be made and patients with a significant risk started on statins
f. All patients receiving steroids should be treated with Calcium and vitamin D, consideration should be given to use of bisphosphonates as per local policy
g. All patients receiving steroids should be treated with GI protection, as per local policy
h. All patients with significant proteinuria should receive angiotensin blockade therapy if no contra-indications, as per local policy
i.

Maintenance therapy for patients on dialysis

a. If patient has not recovered renal function within 6 infusions of cyclophosphamide induction therapy, consideration should be given to stopping further infusions or repeat biopsy.
b. Consideration should be given to stopping immunosuppressive maintenance therapy after 1 year unless patient has had previous relapses. Immunosuppressants and prednisolone should be stopped sequentially.

References

1. Wester Trejo MAC, Flossmann O, Westman KW, Hoglund P, Hagen EC, Walsh M, et al. Renal relapse in antineutrophil cytoplasmic autoantibody-associated vasculitis: unpredictable, but predictive of renal outcome. Rheumatology (Oxford). 2019;58(1):103-9.
2. Walsh M, Flossmann O, Berden A, Westman K, Hoglund P, Stegeman C, et al. Risk factors for relapse of antineutrophil cytoplasmic antibody-associated vasculitis. Arthritis Rheum. 2012;64(2):542-8.
3. Specks U, Merkel PA, Seo P, Spiera R, Langford CA, Hoffman GS, et al. Efficacy of remission-induction regimens for ANCA-associated vasculitis. N Engl J Med. 2013;369(5):417-27.
4. 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. 2016;75(9):1583-94.
5. Smith RM, Jones RB, Specks U, Bond S, Nodale M, Aljayyousi R, et al. A Randomized, Controlled Trial of Rituximab versus Azathioprine After Induction of Remission with Rituximab for Patients with ANCA-associated Vasculitis and Relapsing Disease [abstract]. Arthritis & rheumatology (Hoboken, NJ. 2019;71:https://acrabstracts.org/abstract/a-randomized-controlled-trial-of-rituximab-versus-azathioprine-after-induction-of-remission-with-rituximab-for-patients-with-anca-associated-vasculitis-and-relapsing-disease.
6. Charles P, Terrier B, Perrodeau E, Cohen P, Faguer S, Huart A, et al. 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. 2018;77(8):1143-9.
7. Pagnoux C MA, Hamidou MA, Boffa JJ, Ruivard M, Ducroix JP, Kyndt X, Lifermann F, Papo T, Lambert M, Le Noach J, Khellaf M, Merrien D, Puéchal X, Vinzio S, Cohen P, Mouthon L, Cordier JF, Guillevin L for the French Vasculitis Study Group. Azathioprine or methotrexate maintenance for ANCA-associated vasculitis. N Engl J Med. 2008;359(26):2790-803.
8. Puechal X, Pagnoux C, Perrodeau E, Hamidou M, Boffa JJ, Kyndt X, et al. Long-Term Outcomes Among Participants in the WEGENT Trial of Remission-Maintenance Therapy for Granulomatosis With Polyangiitis (Wegener's) or Microscopic Polyangiitis. Arthritis & rheumatology (Hoboken, NJ. 2016;68(3):690-701.
9. Walters GD, Willis NS, Cooper TE, Craig JC. Interventions for renal vasculitis in adults. Cochrane Database Syst Rev. 2020;1:CD003232.
10. Charles P, Perrodeau E, Samson M, Bonnotte B, Neel A, Agard C, et al. Long-Term Rituximab Use to Maintain Remission of Antineutrophil Cytoplasmic Antibody-Associated Vasculitis: A Randomized Trial. Ann Intern Med. 2020.
11. Sanders JS, de Joode AA, DeSevaux RG, Broekroelofs J, Voskuyl AE, van Paassen P, et al. Extended versus standard azathioprine maintenance therapy in newly diagnosed proteinase-3 anti-neutrophil cytoplasmic antibody-associated vasculitis patients who remain cytoplasmic anti-

neutrophil cytoplasmic antibody-positive after induction of remission: a randomized clinical trial. Nephrol Dial Transplant. 2016;31(9):1453-9.
12. Karras A, Pagnoux C, Haubitz M, Groot K, Puechal X, Tervaert JWC, et al. Randomised controlled trial of prolonged treatment in the remission phase of ANCA-associated vasculitis. Ann Rheum Dis. 2017;76:1662-8.
13. de Joode AAE, Sanders JSF, Puechal X, Guillevin LP, Hiemstra TF, Flossmann O, et al. Long term azathioprine maintenance therapy in ANCA-associated vasculitis: combined results of long-term follow-up data. Rheumatology (Oxford). 2017;56(11):1894-901.
14. Robson J, Doll H, Suppiah R, Flossmann O, Harper L, Hoglund P, et al. Glucocorticoid treatment and damage in the anti-neutrophil cytoplasm antibody-associated vasculitides: long-term data from the European Vasculitis Study Group trials. Rheumatology (Oxford). 2015;54(3):471-81.
15. 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 & research. 2010;62(8):1166-73.
16. McGregor JG, Hogan SL, Hu Y, Jennette CE, Falk RJ, Nachman PH. Glucocorticoids and relapse and infection rates in anti-neutrophil cytoplasmic antibody disease. Clin J Am Soc Nephrol. 2012;7(2):240-7.
17. Mohammad AJ, Segelmark M, Smith R, Englund M, Nilsson JA, Westman K, et al. Severe Infection in Antineutrophil Cytoplasmic Antibody-associated Vasculitis. J Rheumatol. 2017;44(10):1468-75.