Induction of Remission 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 inducing 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 inducing remission in ANCA-associated vasculitis.

Background

The ANCA associated vasculitides (AAV) are a group of systemic, autoimmune inflammatory conditions. They are primary small vessel vasculitides, and are characterised by the presence of circulating anti-neutrophil cytoplasm antibodies (ANCA) and a lack of immune complex deposition. The AAV are typified by necrotising inflammation affecting small to medium blood vessels leading to end organ damage, commonly affecting the kidneys, lungs and upper airways, skin, eyes, joints and nervous system. Pulmonary haemorrhage occurs in 10% of patients.The AAV include granulomatosis with polyangiitis (GPA; previously known as Wegener's granulomatosis), microscopic polyangiitis (MPA), eosinophilic granulomatosis with polyangiitis (EGPA; previously known as Churg-Strauss) and renal limited vasculitis (RLV). About 90% of patients with small-vessel vasculitis have ANCA, directed primarily to the neutrophil granule proteins MPO or PR3. Patients who have pauci-immune necrotising glomerulonephritis should be treated similarly to those who are ANCA positive.

The principles of treatment in AAV are to induce and maintain remission utilising the minimum necessary immunosuppression that is appropriate to disease severity. Induction of remission is achieved by the use of highly potent immunosuppressive agents that generally target T-cells or B-cells [1].

Induction immunosuppressant

In generalised disease, use of pulsed cyclophosphamide (CYC) therapy as opposed to daily oral CYC in addition to oral glucocorticoids (GC) was shown to be equivalent in terms of achieving remission (CYCLOPS trial)[2]. Patients in the pulsed CYC arm received a lower cumulative dose of CYC and had fewer episodes of leucopoenia; however long-term follow up revealed a higher risk of relapse in the pulsed group, although rates of renal failure and mortality were equivalent[3]. A recent retrospective study showed that pulsed CYC in addition to high dose GC and plasma exchange (PEX) was associated with a favourable

outcome when compared to the MEPEX arm that received daily oral CYC suggesting that pulsed CYC is a viable alternative also in severe disease to reduce cumulative dose of CYC and ensuing toxicity[4].

Two recent trials considered the monoclonal anti-CD20 antibody rituximab (RTX) as an alternative to CYC for induction of disease remission in patients with generalised or severe AAV. RITUXVAS (An International, Randomised, Open-label, Trial Comparing a Rituximab Based Regimen with a Standard Cyclophosphamide / Azathioprine Regimen in the Treatment of Active, "Generalised" AAV)[5] and RAVE (Rituximab in ANCA-Associated Vasculitis)[6] had important differences in their methodology, however both trials concluded that RTX was at least as effective as CYC in achieving remission whilst the rate of adverse events including infection were comparable between RTX and CYC treated patients.

Alternative immunosuppressants include methotrexate or mycophenolate for those with limited or who are not considered to have organ threatening disease[7, 8].

Use of plasma exchange

In the management of severe life-threatening disease, the Methylprednisolone Versus Plasma Exchange as Additional Therapy for Severe ANCA-Associated Glomerulonephritis (MEPEX) trial, randomised patients with serum creatinine > 500 μmol/L to receive either three 1g infusions of methylprednisolone on consecutive days or seven 60 mL/kg treatments of PEX within 14 days[9]. All patients also received high dose oral GC and daily oral CYC for induction of remission followed by azathioprine for maintenance of remission. Patients randomised to the PEX arm exhibited better renal recovery and this difference was maintained at 12 months although subsequent long-term follow up has shown no difference between the two arms in terms of survival or renal function at a median follow-up of 3.95 years[10]. However, the much larger PEXIVAS trial (The Plasma Exchange and Glucocorticoid Dosing in the Treatment of AAV: an International Randomised Controlled Trial)[11] which recruited patients with eGFR<50ml/min or with pulmonary haemorrhage showed no difference in The primary end-point of death or ESRD which occurred in 28% in the PLEX group compared with 31% in the no-PLEX group (hazard ratio 0.86, 95% CI: 0.65, 1.13; *P* =0.27) demonstrating that the addition of PLEX along with standard therapy neither saved lives nor avoided ESRD.

Corticosteroid use

Glucocorticoids have the advantage of acting rapidly and are of undeniable efficacy in the short term. They have been considered a ubiquitous part of therapy, despite their toxicities, such as metabolic effects and diabetes, osteoporosis, psychiatric disorders and an increased risk of infections.

High-dose glucocorticoids have been a mainstay of induction therapy[12]. Contemporary approaches to treatment have focused on limiting glucocorticoid exposure but there is limited consensus of

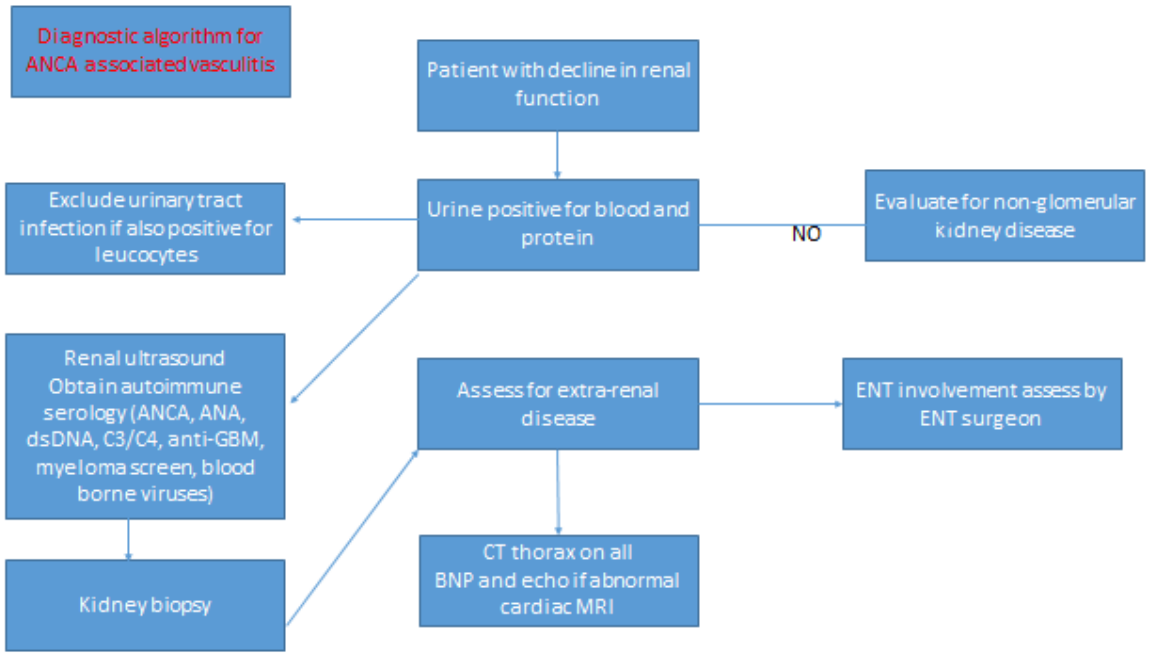
tapering schedule. Data on the benefits of i.v. methylprednisolone are limited and evidence for associated harm has accrued more recently.

PEXIVAS investigated two prednisolone induction regimens[11]. All individuals received methylprednisolone 1-3g prior to randomisation. Patients on the reduced-dose regimen received 54% of the cumulative amount of glucocorticoids of the standard-dose group through the first 3 months, and 61% over the course of 6 months. Death from any cause or ESKD occurred in 92 of 330 patients (27.9%) in the reduced-dose group and in 83 of 325 patients (25.5%) in the standard-dose group (absolute risk difference, 2.3 percentage points; 90% CI, −3.4 to 8.0), which met the criterion for noninferiority. Serious infections at 1 year were less common in the reduced-dose group than in the standard-dose group (incidence rate ratio, 0.69; 95% CI, 0.52 to 0.93), but other secondary outcomes were similar in the two groups.

A recent retrospective multi-centre study has shown that the use of intravenous pulse methylprednisolone in addition to CYC and standard high dose oral GC to induce remission in severe life-threatening AAV does not confer any additional benefit in terms of overall survival, renal recovery or relapse risk at 12 months but is associated with increased incidence of infection in the first 3 months and a higher incidence of new-onset diabetes mellitus[13].

Guideline

Diagnostic algorithm



The kidney biopsy gives prognostic information, however induction treatment should not be withheld on the basis of an unfavourable biopsy.

Treatment strategy (Figure 2)

a. New onset of organ-threatening or life-threatening AAV should be treated with a combination of high dose oral glucocorticoids (GC) **AND** rituximab (RTX). Rituximab will be used as first line while there are concerns about hospital attendance and COVID risk.
b. Cyclophosphamide should be used instead of rituximab at present only where rituximab is contra-indicated or previously shown to be inadequate therapy.
c. All patients with AAV should be considered to have potentially organ-threatening or life-threatening disease unless there is clear evidence that disease is limited to the upper respiratory tract.
d. Methotrexate (MTX) or mycophenolate mofetil (MMF) are alternative remission induction agents for patients with limited disease, low disease activity and no risk of organ damage. In practice, the vast majority of patients (and in the case of patients managed by nephrology, all patients) will have at least organ-threatening disease and should therefore be managed with GC and either CYC or RTX. Methotrexate should not be used in patients with impaired kidney function.
e. Following the PEXIVAS trial results plasma exchange (PEX) should not be routinely used for induction of remission in AAV. PEX should still be considered for patients with dual anti-GBM / ANCA positivity. Consideration to use of PEX if creatinine>500umol/l and slow response to treatment. Must be discussed with vasculitis team.
f. Where the clinical presentation compatible with small-vessel vasculitis in combination with positive MPO- or PR3-ANCA serology, waiting for a kidney biopsy to be performed or reported should not delay starting immunosuppressive therapy, especially in patients who are rapidly deteriorating.

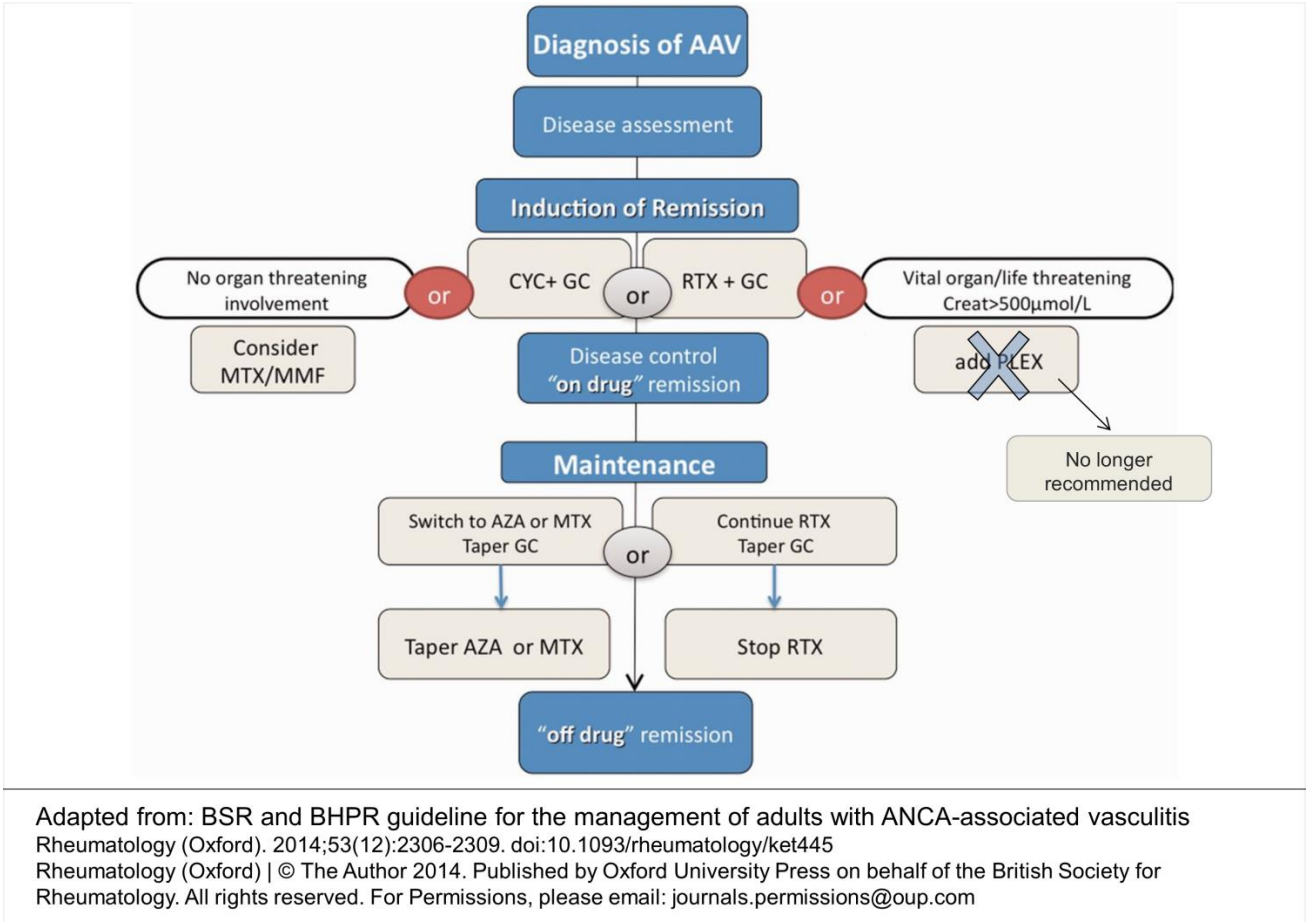


Figure 2 AAV treatment strategy

1. **High dose oral glucocorticoids**
    a. High dose oral glucocorticoids (GC) should be commenced without delay once a clinical diagnosis has been made at a dose of 1mg/kg (maximum starting dose 60mg OD) (Table 1)
    b. Intravenous pulse methylprednisolone should not be routinely used for induction of remission. Use of methylprednisolone is not evidenced based and likely to contribute to steroid toxicity[13]Where patients have received intravenous pulse methylprednisolone of 500mg or more in other centres prior to being transferred over, the dose of oral GC should commence at 0.5mg/kg (Table 1)
    c. Proton pump inhibitor therapy (e.g. lansoprazole 30mg daily) or H2 receptor blocker therapy (e.g. Ranitidine 150mg BD) should be commenced for gastro-protection.
    d. Oral co-trimoxazole (480mg every other day) should be commenced for PJP prophylaxis. Atovaquone should be considered for PJP prophylaxis in case of co-trimoxazole allergy or intolerance, while receiving induction therapy or corticosteroid dose is >10mg.
    e. Topical or systemic anti-fungal therapy should not be routinely prescribed for prophylaxis unless specifically indicated.

f. A FRAX assessment should be made to assess fracture risk. In those at high risk, bone protective treatment should be considered as recommended by the National Osteoporosis Guideline Group 2017.
g. Patients receiving treatment with high dose glucocorticoids are at risk of developing diabetes mellitus. Random blood glucose and HbA1C should be monitored.

Table 1 Oral glucocorticoid dose protocol for induction of remission in AAV

Time (weeks)	Standard Dose mg/day	Reduced Dose* mg/day
1	60	30
2	45	25
3-4	30	20
5-6	25	15
7-8	20	12.5
9-10	15	10
11-12 (3 months)	12.5	7.5
13-14	10	5
15-16	7.5	5
17-18	5	5
19-20	5	5
21-22	5	5
23-52	5	5

***Only use reduced protocol for patients that have received ≥500mg of intravenous pulse methylprednisolone in other centres prior to being transferred over**

2. Cyclophosphamide

a. Cyclophosphamide (CYC) should be given by intravenous pulses. The dose is 15 mg/kg and should be reduced according to age and renal function (Table 2). A total of 6-10 infusions are usually required to induce remission.
b. CYC infusions should be given every 2 weeks for the first 3 infusions and every 3 weeks thereafter (weeks 0, 2, 4, 7, 10 and 13). After the 6th infusion, a clinical decision needs to be made as to whether disease remission has been satisfactorily achieved or whether further infusions are required. If further infusions are indicated those should continue every 3 weeks up to a maximum of 10 infusions (weeks 16, 19, 22 and 25).
c. Liaise with the renal infusion suite (ext. 2576 or via e-mail) to arrange CYC infusions.
d. Patients must be consented prior to commencing CYC treatment (written consent) and provided with ARUK leaflet and information regarding sperm banking if appropriate.
e. Blood borne virus screen (hepatitis B core antibody, hepatitis B surface antibody, hepatitis B surface antigen, hepatitis C, HIV) must be sent and the result reviewed prior to CYC commencement. If there is evidence of past hepatitis B infection, discuss with liver team and consider commencing lamivudine prophylaxis.

f. It is recommended to check Varicella zoster virus (VZV) IgG status prior to or at the time of commencing CYC treatment although treatment is not contraindicated in VZV IgG negative patients
g. Oral mesna should be administered as per UHB CYC protocol: 400mg pre-infusion, 400mg 2 hours post-infusion, and 400mg 6 hours post-infusion
h. Oral co-trimoxazole (480mg every other day) for PJP prophylaxis should be discontinued once cyclophosphamide infusions are stopped and prednisolone dose<10mg. Atovaquone should be considered in case of co-trimoxazole allergy or intolerance.
i. Full blood count must be monitored closely: 4 days pre-infusion for the first 3 infusions and up to 7 days pre-infusion for subsequent infusions **AND** 10-14 days post-infusion. Infusion dose may need to be adjusted depending on the white cell count 10-14 days post-infusion (see UHB CYC protocol). Infusion should not proceed if pre-infusion white cell count is $< 4 \times 10^9$/L or neutrophil count is $< 2 \times 10^9$/L.
j. Life time exposure to CYC should be ≤25g since the long-term toxicity of CYC is determined by cumulative dose. The cumulative dose should not exceed 10g if preservation of fertility is required
k. In dialysis dependent patients, if renal function has not recovered within 6 infusions of CYC, consideration should be given to stopping further infusions.

Table 2 Cyclophosphamide dosing

Age	eGFR > 30 ml/min/1.73m^2	eGFR < 30 ml/min/1.73m^2
<60	15 mg/kg	12.5 mg/kg
60-70	12.5 mg/kg	10 mg/kg
>70	10 mg/kg	7.5 mg/kg

3. Rituximab

a. Rituximab (RTX) is at least as effective as CYC for remission induction of previously untreated patients and is preferable when CYC avoidance is desirable, such as in young people at risk of infertility and those at high risk of infection.
b. Intravenous rituximab is licensed to treat patients with severe life or organ threatening AAV. NHS England criteria for commissioning are: active, progressive or relapsed disease despite a course of CYC lasting 3-6 months; OR, CYC is contraindicated or not tolerated; OR, the person has not completed their family and treatment with CYC may materially affect their fertility; OR, the person has had uroepithelial malignancy. As frequent hospital attendances increases the risk of COVID 19 in a vulnerable group, we have extended use of rituximab to the preferred induction therapy during this period of uncertainty.
c. RTX should be given as 2 infusions of 1g, 2 weeks apart. The licensed dosing protocol for RTX is 375mg/m^2/week for 4 weeks, however, 2 infusions of 1g each, 2 weeks apart, is equally effective and is the dosing protocol of choice at UHB and the majority of renal units.

d. Liaise with the renal infusion suite (ext. 2576 or via e-mail) to arrange RTX infusions.
e. Blood borne virus screen (hepatitis B core antibody, hepatitis B surface antibody, hepatitis B surface antigen, hepatitis C, HIV) must be sent and the result reviewed prior to RTX commencement. Hepatitis B infection and reactivation (including fatal cases) have been reported in patients taking **rituximab**. Patients with positive hepatitis B serology should be discussed with a liver specialist for monitoring and initiation of antiviral therapy before treatment initiation; immunosuppressive treatment should not be initiated in patients with evidence of current hepatitis B infection until the infection has been adequately treated. Patients should be closely monitored for clinical and laboratory signs of active hepatitis B infection.
f. It is recommended to check Varicella zoster virus (VZV) IgG status prior to or at the time of commencing RTXtreatment although treatment is not contraindicated in VZV IgG negative patients
g. Intravenous methylprednisolone (100mg), piriton 4mg and paracetamol 1g orally should be co-administered with RTX (see also UHB RTX protocol)
h. Oral co-trimoxazole (480mg every other day) for PJP prophylaxis should be continued for 6 months following RTX treatment for remission induction. Atovaquone should be considered in case of co-trimoxazole allergy or intolerance.

4. Relapsing disease

a. Relapsing disease should be treated with an increase in immunosuppression.
b. A minor relapse may be treated with an increase in GC dosage and optimisation of concurrent immunosuppression (e.g. increase in azathioprine dosage).
c. A major relapse should be treated with RTX or CYC re-induction therapy as described above and a temporary increase in GC dosage. Repeated pulses of cyclophosphamide should be avoided due to the risks of malignancy which are dependent on the cumulative dose of cyclophosphamide. A maximum dose of 24g should be used. Rituximab maybe more effective in patients with relapsing disease. In the RAVE study, patients with relapsing disease more often achieved remission at six and 12 months in the rituximab group compared to the cyclophosphamide-azathioprine group.
d. Sinonasal disease should be reviewed by an ENT physician to assess disease inflammation and infection

5. Refractory disease

a. Patients with refractory disease should be discussed in the multi-disciplinary team meeting.
b. For patients with disease refractory to RTX treatment, further induction therapy with cyclophosphamide should be considered or vice versa other options include intravenous immunoglobulin treatment and anti-T cell therapies. Consideration should be given to drivers for refractory disease and the clinical diagnosis should be re-visited.

c. Progression of kidney disease may reflect chronic kidney disease rather than relapse and repeat biopsy should be considered

6. Additional advice

a. For patients of child-bearing age adequate contraception must be used whilst receiving remission induction therapy. For patients wishing to conceive this should be carefully planned at least 12 months following initial diagnosis with consideration of disease stability, altering maintenance immunosuppression and other medication such as anti-hypertensives if necessary, and referral to a pre-conception clinic.

b. Live vaccines should not be administered at any point.

c. Discontinue immunosuppressive therapy after three months in patients who remain dialysis-dependent and who do not have any extra-renal manifestations of disease.

d. Vaccination for pneumococcus and influenza should not be given during induction of remission therapy unless it is possible to give these 4 weeks prior to commencing therapy.

e. Cardiovascular risk should be assessed and patients commenced on statin therapy if appropriate.

f. Blood pressure should be controlled with appropriate anti-hypertensive agents. Patients with significant proteinuria and stable renal function should receive angiotensin blockade therapy if no contra-indications.

g. All patients should receive lifestyle advice (smoking cessation, exercise, healthy diet).

h. All patients with sinonasal disease should be advised to perform regular nasal douching and use of moisturiser to the anterior nares.

i. All patients should be referred to the ANCA vasculitis immunosuppression clinical nurse specialist who will provide patient information leaflets and additional disease counselling.

REFERENCES

1. Ntatsaki E, Carruthers D, Chakravarty K, D'Cruz D, Harper L, Jayne D, Luqmani R, Mills J, Mooney J, Venning M *et al*: **BSR and BHPR guideline for the management of adults with ANCA-associated vasculitis**. *Rheumatology (Oxford)* 2014, **53**(12):2306-2309.
2. de Groot K, Harper L, Jayne D, Flores Suarez L, Gregorini G, Gross W, al e, , Group). EEVS: **Pulse versus daily oral cyclophosphamide for induction of remission in antineutrophil cytoplasmic antibody--associated vasculitis. A randomized trial.** . *Ann Intern Med* 2009, **150**:670-680.
3. Harper L, Morgan MD, Walsh M, Hoglund P, Westman K, Flossmann O, Tesar V, Vanhille P, de Groot K, Luqmani R *et al*: **Pulse versus daily oral cyclophosphamide for induction of remission in ANCA-associated vasculitis: long-term follow-up**. *Ann Rheum Dis* 2012, **71**(6):955-960.
4. Pepper RJ, Chanouzas D, Tarzi R, Little MA, Casian A, Walsh M, Pusey CD, Harper L, Salama AD, European Vasculitis Study i: **Intravenous cyclophosphamide and plasmapheresis in dialysis-dependent ANCA-associated vasculitis**. *Clin J Am Soc Nephrol* 2013, **8**(2):219-224.

5. Jones RB, Tervaert JW, Hauser T, Luqmani R, Morgan MD, Peh CA, Savage CO, Segelmark M, Tesar V, van Paassen P *et al*: **Rituximab versus cyclophosphamide in ANCA-associated renal vasculitis**. *N Engl J Med* 2010, **363**(3):211-220.
6. Stone JH, Merkel PA, Spiera R, Seo P, Langford CA, Hoffman GS, Kallenberg CG, St Clair EW, Turkiewicz A, Tchao NK *et al*: **Rituximab versus cyclophosphamide for ANCA-associated vasculitis**. *N Engl J Med* 2010, **363**(3):221-232.
7. de Groot K, Rasmussen N, Bacon PA, Tervaert JW, Feighery C, Gregorini G, Gross WL, Luqmani R, Jayne DR: **Randomized trial of cyclophosphamide versus methotrexate for induction of remission in early systemic antineutrophil cytoplasmic antibody-associated vasculitis**. *Arthritis Rheum* 2005, **52**(8):2461-2469.
8. Jones RB, Hiemstra TF, Ballarin J, Blockmans DE, Brogan P, Bruchfeld A, Cid MC, Dahlsveen K, de Zoysa J, Espigol-Frigole G *et al*: **Mycophenolate mofetil versus cyclophosphamide for remission induction in ANCA-associated vasculitis: a randomised, non-inferiority trial**. *Ann Rheum Dis* 2019, **78**(3):399-405.
9. Jayne DR, Gaskin G, Rasmussen N, Abramowicz D, Ferrario F, Guillevin L, Mirapeix E, Savage CO, Sinico RA, Stegeman CA *et al*: **Randomized trial of plasma exchange or high-dosage methylprednisolone as adjunctive therapy for severe renal vasculitis**. *J Am Soc Nephrol* 2007, **18**(7):2180-2188. Epub 2007 Jun 2120.
10. Walsh M, Casian A, Flossmann O, Westman K, Hoglund P, Pusey C, Jayne DR, European Vasculitis Study G: **Long-term follow-up of patients with severe ANCA-associated vasculitis comparing plasma exchange to intravenous methylprednisolone treatment is unclear**. *Kidney Int* 2013, **84**(2):397-402.
11. Walsh M, Merkel PA, Peh CA, Szpirt WM, Puechal X, Fujimoto S, Hawley CM, Khalidi N, Flossmann O, Wald R *et al*: **Plasma Exchange and Glucocorticoids in Severe ANCA-Associated Vasculitis**. *N Engl J Med* 2020, **382**(7):622-631.
12. Yates M, Watts RA, Bajema IM, Cid MC, Crestani B, Hauser T, Hellmich B, Holle JU, Laudien M, Little MA *et al*: **EULAR/ERA-EDTA recommendations for the management of ANCA-associated vasculitis**. *Ann Rheum Dis* 2016, **75**(9):1583-1594.
13. Chanouzas D, McGregor JAG, Nightingale P, Salama AD, Szpirt WM, Basu N, Morgan MD, Poulton CJ, Draibe JB, Krarup E *et al*: **Intravenous pulse methylprednisolone for induction of remission in severe ANCA associated Vasculitis: a multi-center retrospective cohort study**. *BMC nephrology* 2019, **20**(1):58.