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Guidelines

BSR and BHPR guideline for the management of adults with ANCA-associated vasculitis

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Key words: vasculitis, guideline, management, cyclophosphamide, rituximab.

Executive summary

Scope and purpose of the guideline

The ANCA-associated vasculitides (AAVs) are heterogeneous, multisystem disorders characterized by inflammation and necrosis of small and medium blood vessels with unknown aetiology. Three distinct clinico-pathological syndromes have been identified: granulomatosis with polyangiitis (GPA), eosinophilic granulomatosis with polyangiitis and microscopic polyangiitis. The Chapel Hill Consensus Conference (CHCC) in 2012 updated the definitions, however, there are still no validated diagnostic criteria. The aim of this document is to provide guidelines for the management of adults with AAV.

The target audience is rheumatologists, nephrologists, general physicians, specialists, trainees and nurse practitioners. The guideline does not cover the management of other systemic vasculitides or the treatment of children.

This is a short summary of the guideline. The full guideline is available as supplementary material, available at *Rheumatology* Online. For definitions of levels of evidence and recommendation strength see Tables 1 and 2.

Guideline for the management of adults with AAV

We have produced evidence-based recommendations for treatment, giving a grade of recommendation (from A to D) and an algorithm to illustrate the approach to the management of a patient with newly diagnosed AAV.

NICE has accredited the process used by the BSR to produce its guidance for the management of ANCA-associated vasculitis in adults. Accreditation is valid for 5 years from 10 June 2013. More information on accreditation can be viewed at www.nice.org.uk/accreditation. For full details on our accreditation visit: www.nice.org.uk/accreditation.

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Table 1 Level of evidence

Category	Evidence
Ia	From meta-analysis of randomized controlled trials
Ib	From at least 1 randomized controlled trial
IIa	From at least 1 controlled study without randomization
IIb	From at least 1 type of quasi-experimental study
III	From descriptive studies, such as comparative studies, correlation studies, or case–control studies
IV	From expert committee reports or opinions and/or clinical experience of respected authorities

Table 2 Determination of recommendation strength

Strength	Directly based on
A	Category 1 evidence
B	Category 2 evidence or extrapolated recommendations from category 1 evidence
C	Category 3 evidence or extrapolated recommendations from category 1 or 2 evidence
D	Category 4 evidence or extrapolated recommendations from category 2 or 3 evidence

Eligibility criteria

Patients with disease consistent with the definitions of ANCA vasculitis as defined by the CHCC in 2012 are eligible for treatment and use of this guideline.

Exclusion criteria

For a diagnosis of ANCA vasculitis, it is important to exclude other causes of systemic illness such as malignancy, systemic infection, drugs, secondary vasculitides or mimics.

Definition of disease states

Remission: well-controlled disease.

(i) On drug remission: prednisolone dose $\leqslant$10 mg/day and a BVAS $\leqslant$1 for $\geqslant$6 months.
(ii) Drug-free remission: $\geqslant$6 months off all treatment for vasculitis.

Relapsing: disease that has been previously well controlled with or without drugs and has become active.

Minor relapse: increase of one or more new or worse minor items and no major BVAS items.

Major relapse: increase of one or more major BVAS item.

Refractory: progressive disease that is unresponsive to current therapy, i.e. remission is not achieved.

Treatment

All patients with AAV should be considered to have severe, potentially life- or organ-threatening disease. Treatment regimens are divided into induction, maintenance and long-term follow-up. Patients who relapse may require a further course of induction therapy (secondary).

The essential principles of management are

(i) Rapid diagnosis
(ii) Rapid initiation of treatment
(iii) Early induction of remission to prevent organ damage
(iv) Maintenance of remission with the aim of eventual drug withdrawal
(v) Prevention of drug toxicity

Primary induction of remission

All patients with newly diagnosed AAV should be assessed for treatment with glucocorticoids (GCs) and i.v. pulse cyclophosphamide (CYC) or rituximab (RTX) (A) (Fig. 1).

Cyclophosphamide

CYC should be given by i.v. pulses initially at 2-week intervals and then at 3-week intervals following the CYCLOPS trial regimen (A). The standard dose is 15 mg/kg, reduced for age and renal function. Because of the lower toxicity, the i.v. regimen is preferred (B). Each individual course of CYC should be $\geqslant$3 months and $\leqslant$6 months (B). Lifetime exposure to CYC should be $\leqslant$25 g since the long-term toxicity of CYC is determined by cumulative dose (C). Patients on CYC should be monitored regularly and the dose should be reduced if there is CYC-induced leucopenia/neutropenia (B). Patients intolerant to CYC can be effectively treated with RTX (B).

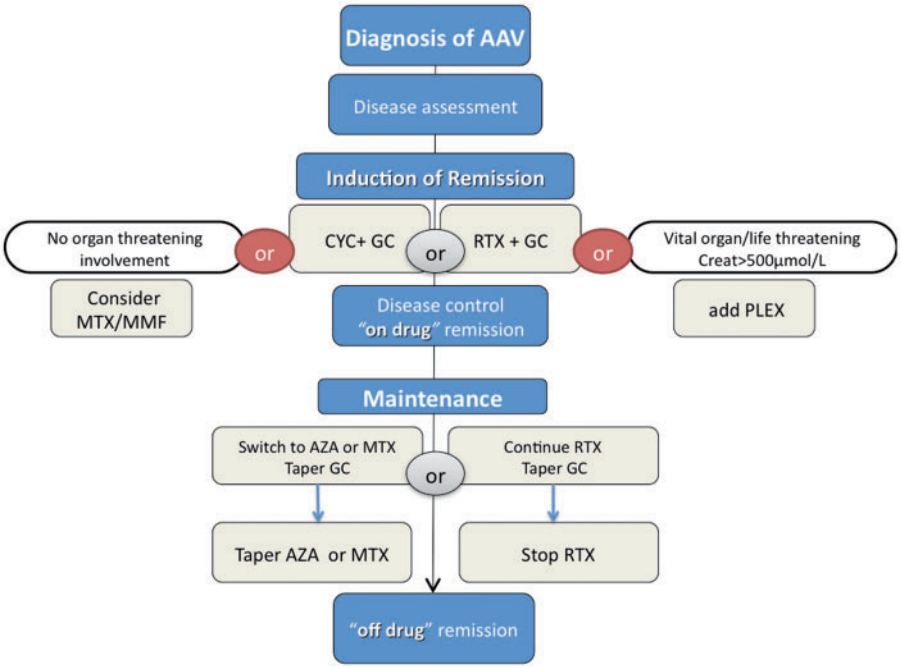
Rituximab

RTX is 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). The licensed RTX dosing protocol is 375 mg/m^2/week for 4 weeks (B), however, 1 g repeated after 2 weeks is equally effective (C).

MTX and MMF

MTX (up to 25–30 mg/week) and MMF (up to 3 g/day) are alternative remission induction agents for patients with

Fig. 1 Algorithm of the treatment guideline for AAV



evidence of low disease activity and not at risk of suffering organ damage as assessed by the BVAS (A). MTX should not be used in patients with moderate or severe renal impairment (B). MMF may be an alternative to MTX (B).

Plasma exchange

Patients with AAV presenting with severe renal failure (creatinine >500 μmol/l) should be treated with pulsed CYC and GCs, with adjuvant plasma exchange in a centre experienced in its use (B). Treatment with plasma exchange should also be considered in those with other life-threatening manifestations of disease, such as pulmonary haemorrhage (C).

Glucocorticoids

Induction therapy for AAV includes treatment with high-dose GCs in combination with another immunosuppressive agent (CYC, RTX) (A).

GCs are usually given as daily oral prednisolone, initially at relatively high doses (1 mg/kg up to 60 mg) (B) with the dose rapidly reduced to 15 mg prednisolone at 12 weeks (C). Longer courses of GCs may cause increased risk of infection, but may be associated with fewer relapses (A). GC i.v. infusions (250–500 mg methyl-prednisolone) are sometimes given just prior to or with the first two pulses of CYC (C).

Maintenance therapy

Following successful remission, CYC should be withdrawn and substituted with either AZA or MTX (A). MMF (C) or LEF (B) may be used as alternatives for intolerance to or lack of efficacy of AZA or MTX. Patients should continue maintenance therapy for at least 24 months following successful disease remission (B). Patients with GPA or patients who remain PR3-ANCA positive should continue immunosuppression for up to 5 years (C).

RTX may also be used as maintenance therapy, and re-treatment can be decided based on fixed-interval regimens or evidence of relapse (C). The recommended RTX regimen uses 1 g every 4–6 months for 2 years (B).

Withdrawal of treatment

Patients in continual remission for at least 1 year on maintenance therapy should be considered for tapering of GC treatment (D).

Following GC withdrawal, other immunosuppressive therapy may be withdrawn after 6 months (D).

Relapsing disease

Relapsing disease should be treated with an increase in immunosuppression. A minor relapse may be treated with an increase in prednisolone dosage and optimization of concurrent immunosuppression (C). A major relapse may be treated with RTX (A) or CYC with an increase in prednisolone (B). The addition of i.v. methylprednisolone or plasma exchange may also be considered (C). Drivers for relapse need to be identified and addressed and may include infection, malignancy and change of drug therapy (D).

Refractory disease

Refractory disease should only be treated in close collaboration with expert/tertiary centres via a hub-and-spoke

model (D). RTX is more effective than CYC in refractory AAV (A). If the patient has not had previous treatment with RTX, then the first choice is RTX (A). Drivers for refractory disease should be sought and clinicians should consider revision of the clinical diagnosis (D).

Assessment and monitoring of disease status

Validated tools [such as the BVAS, Vasculitis Damage Index (VDI) and 36-item Short Form (SF-36)] should be used by trained staff to assess disease activity, extent of damage and quality of life (D). ANCA should be detected using IIF with ELISA to confirm PR3 or MPO specificity (C) and checked at diagnosis, relapse, change of therapy, every 6 months while on treatment and annually while off treatment (B). Results should be available within 1 working day (D). Treatment should not be escalated solely on the basis of an increase in ANCA (B).

Detection and prevention of potential adverse effects of immunosuppressive therapy

The following recommendations should be considered for patients with AAV on immunosuppressive therapy:

(i) Routine blood test monitoring [full blood count (FBC), urea and electrolytes (U&Es), liver function tests (LFTs)] (C)
(ii) Regular urinalysis and mesna for protection against CYC-induced urothelial toxicity (C)
(iii) Serum immunoglobulin measurement before each cycle of RTX therapy (C)
(iv) Trimethoprim/sulfamethoxazole as prophylaxis against *Pneumocystis jiroveci* (B)
(v) Antifungal prophylaxis (C)
(vi) *Staphylococcal aureus* treatment with long-term nasal mupirocin (C)
(vii) Screening for cervical intraepithelial neoplasia (CIN) (female patients) (C)
(viii) Counselling about the possibility of infertility following CYC treatment (C)
(ix) Prophylaxis against osteoporosis where appropriate (A)
(x) Tuberculosis screening (C)
(xi) Vaccination against pneumococcal infection, influenza and hepatitis B (C)
(xii) Cardiovascular and thromboembolic risk assessment (C)

Patient involvement and education

Patients should receive ongoing, tailored education and information about AAV and be encouraged to engage in self-monitoring to improve treatment compliance and long-term outcomes (D). They should have access to information about alternative and complementary therapies that might provide symptomatic relief (D).

Overview of care, collaboration and access to specialist services

Patients with AAV should be managed by a nominated clinician within clinical networks linked with centres of expertise and other specialities within the local organization (D). People with a suspected diagnosis of systemic vasculitis should be rapidly assessed by a specialist physician with an expertise in vasculitis (D). Self-referral mechanisms should be in place for patients, enabling rapid access to a specialist when flaring occurs (D).

Vasculitis annual review, research, audit and registries

Patients with AAV require long-term follow-up and should be encouraged to take part in studies and registries (D). Their annual review should follow a structured format. Audits may need to be conducted on a collaborative basis and may be focused on service delivery and patient-specific areas.

Key quality standards

Rapid access to specialist physicians.
Access to multidisciplinary team.
Provision of personalized education about the disease and its effects.
Access to a full range of therapies.
Opportunity to participate in registries and research projects.

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