

## Guidelines



# BSR and BHPR guidelines for the management of adults with ANCA associated vasculitis

C. Lapraik<sup>1</sup>, R. Watts<sup>2,3</sup>, P. Bacon<sup>4</sup>, D. Carruthers<sup>5</sup>, K. Chakravarty<sup>6</sup>, D. D'Cruz<sup>7</sup>, L. Guillevin<sup>8</sup>, L. Harper<sup>9</sup>, D. Jayne<sup>10</sup>, R. Luqmani<sup>11</sup>, J. Mooney<sup>12</sup>, D. Scott<sup>1,2</sup>  
on behalf of the BSR and BHPR Standards, Guidelines and Audit Working Group

**KEY WORDS:** Vasculitis, Guideline, Management, Cyclophosphamide.

### Executive summary

#### *Scope and purpose of the guideline*

The ANCA associated vasculitides (AAV) comprise a group of conditions characterized by inflammation and necrosis of small and medium-sized blood vessels. They comprise Wegener's granulomatosis, Churg–Strauss syndrome and microscopic polyangiitis. Early diagnosis and treatment is important as the presence of advanced disease at diagnosis limits the potential benefit of therapy. The aim of this document is to provide guidelines for the management of adults with systemic vasculitis. The guidelines concentrate on the indications for using cyclophosphamide and the different therapeutic regimens available. The guideline does not cover the treatment of children or other types of systemic vasculitis. The target audience is rheumatologists, nephrologists and general physicians, together with trainees and nurse practitioners.

This is a short summary of the whole guideline. The full guideline is available on the journal website.

<sup>1</sup>Department of Rheumatology, Norfolk and Norwich University Hospital, Norwich, UK, <sup>2</sup>School of Medicine Health Policy and Practice, University of East Anglia, Norwich, UK, <sup>3</sup>Department of Rheumatology, Ipswich Hospital NHS Trust, Ipswich, UK, <sup>4</sup>Department of Rheumatology, University of Birmingham, Birmingham, UK, <sup>5</sup>Department of Rheumatology, City Hospital, Birmingham, UK, <sup>6</sup>Department of Rheumatology, Harrold Wood Hospital, London, UK, <sup>7</sup>Department of Rheumatology, St Thomas's Hospital, London, UK, <sup>8</sup>Department of Internal Medicine, Hôpital Cochin, Université Paris-René-Descartes, France, <sup>9</sup>Department of Nephrology, Queen Elizabeth Hospital, Birmingham, UK, <sup>10</sup>Department of Nephrology, Addenbrooke's Hospital, Cambridge, UK, <sup>11</sup>Department of Rheumatology, Nuffield Orthopaedic Centre and University of Oxford, Oxford, UK and <sup>12</sup>School of Nursing and Midwifery, University of East Anglia, Norwich, UK.

Submitted 3 November 2006; revised version accepted 24 April 2007.

Correspondence to: Dr Richard Watts, Consultant Rheumatologist, Ipswich Hospital NHS Trust, Heath Road, Ipswich IP4 5PD, UK.  
E-mail: Richard.watts@ipswichhospital.nhs.uk

### Guideline for the management of adults with ANCA-associated vasculitis

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

#### *Eligibility criteria*

Eligibility for treatment and use of this guideline depends on the assumption that a definite diagnosis of vasculitis has been made. The following criteria must be fulfilled prior to a diagnosis of vasculitis:

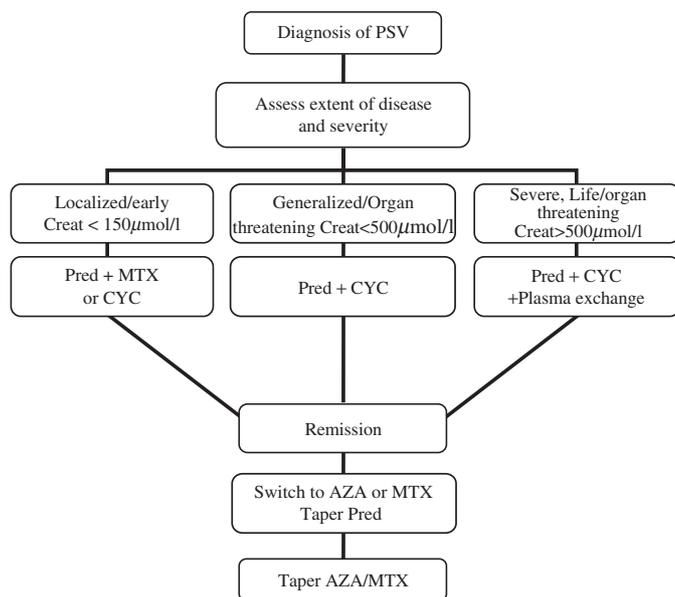
- A. Symptoms and signs characteristic of systemic vasculitis.
- B. At least one of the following:
  1. Histological evidence of vasculitis and/or granuloma formation,
  2. Positive serology for ANCA (either cANCA/PR3 or pANCA/MPO),
  3. Specific indirect evidence of vasculitis.
- C. No other diagnosis to account for symptoms or signs.

#### *Exclusion criteria*

It is important to consider other causes of systemic illness, especially malignancy, infection (particularly bacterial endocarditis) and drugs.

#### *Treatment*

Treatment for vasculitis requires induction of remission followed by maintenance (A). Current treatment is based on assessing the severity and extent of disease and subdividing the disease into three groups: (i) localized and/or early, (ii) generalized disease with threatened organ involvement and (iii) severe/life threatening disease (C).



Algorithm of guideline.

### 1. Localized/early systemic disease

Treatment should be with either cyclophosphamide or methotrexate. Methotrexate may be associated with a higher relapse rate (A). Evidence of progression or relapse should be treated with cyclophosphamide (B). Localized disease can cause significant local destruction and requires treatment with cyclophosphamide treatment (C).

### 2. Generalized/threatened organ involvement

Initial treatment of generalized/organ threatening disease should include cyclophosphamide and steroids (A). Cyclophosphamide may be given as continuous low dose oral treatment or by intravenous pulses initially at 2-week intervals and then 3 weekly (A). There is no difference in remission rates and no increased risk of relapse between IV and oral regimens (A). Continuous low dose oral cyclophosphamide was associated with a higher total cyclophosphamide dosage and a significant increase in infection risk. Transfer to maintenance therapy at 3 months when receiving continuous low dose oral cyclophosphamide and at 3–6 months when receiving pulsed intravenous cyclophosphamide if successful disease remission has been achieved (A). In both cases, the aim should be for a maximum duration of therapy of 6 months where successful disease remission has been achieved.

### 3. Severe/life threatening disease

Patients with AAV presenting with severe renal failure (creatinine  $>500 \mu\text{mol/l}$ ) should be treated with cyclophosphamide (either pulsed IV or continuous low dose oral) and steroids, with adjuvant plasma exchange (A). Plasma exchange should also be considered in those with other life threatening manifestations of disease such as pulmonary haemorrhage (C).

### 4. Steroids

Steroids are usually given as daily oral prednisolone. Initially at relatively high doses; 1 mg/kg up to 60 mg (A). Intravenous steroids (250–500 mg methylprednisolone) are sometimes given just prior to/with the first two pulses of cyclophosphamide (A).

### 5. Patients intolerant of cyclophosphamide

For cases where patients are intolerant of cyclophosphamide, alternative treatments such as methotrexate, azathioprine, leflunomide or mycophenolate mofetil may be used (B,C).

### 6. Maintenance therapy

Following achievement of successful remission, cyclophosphamide should be withdrawn and substituted with either azathioprine or methotrexate (A). Mycophenolate or leflunomide may be used as alternatives for intolerance or lack of efficacy of azathioprine or methotrexate (C). Patients should continue maintenance therapy for at least 24 months following successful disease remission (B). Patients with Wegener's granulomatosis or patients who remain ANCA positive should continue immunosuppression for up to 5 years (C).

### 7. Relapsing disease

Minor relapse is treated with an increase in prednisolone dosage and optimization of concurrent immunosuppression (C). Major relapse is treated with cyclophosphamide with an increase in prednisolone; intravenous methylprednisolone or plasma exchange may also be considered (C).

### 8. Refractory disease

The use of infliximab, intravenous immunoglobulin, antithymocyte globulin, CAMPATH-1H (alemtuzumab, anti-CD52), deoxyspergualin and rituximab in refractory disease is still under investigation (C). It is important to identify potential underlying factors influencing persistent or relapsing disease including infection and malignancy.

### 9. Assessment and monitoring of disease activity

Relapse may occur at anytime after diagnosis and remission induction. A validated tool should be used to assess disease activity and extent of disease (C). ANCA measurements are not closely associated with disease activity. Treatment should not be escalated solely on the basis of an increase in ANCA (B). Treatment withdrawal in patients with persistently positive ANCA is associated with relapse.

### 10. Detection and prevention of potential adverse effects of immunosuppressive therapy

1. Mesna should be considered for protection against urothelial toxicity (C).
2. Trimethoprim/sulfamethoxazole (or aerosolized pentamidine) should be used as prophylaxis against pneumocystis jiroveci (B,C).
3. Antifungal prophylaxis treatment should be used (C).
4. Staphylococcal aureus treatment with long-term nasal mupirocin should be considered (C).
5. Female patients should be screened for cervical intraepithelial neoplasia (CIN) (C).
6. Patients should be counselled about the possibility of infertility following cyclophosphamide treatment (C).
7. Prophylaxis against osteoporosis should be used on all patients receiving high dose corticosteroids (C).
8. Patients receiving immunosuppression should be screened for TB (C).
9. Patients receiving immunosuppression should be vaccinated against pneumococcal infection and influenza (C).
10. Cardiovascular and thromboembolic risk should be assessed (C).

### 11. Audit

This should include relapse rate, infection rate, mortality and cumulative doses of cyclophosphamide.